Mechanism of Action of Atracurium on Airways

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Histamine-releasing drugs may produce significant effects on airways in high-risk populations. To determine if clinically relevant doses of atracurium produce adverse effects on airways, we measured changes in airway resistance in the lung periphery of anesthetized Basenji-Greyhound dogs before and after intravenous (iv) administration of atracurium. A wedged bronchoscope technique was used to measure collateral system resistance (R_{cs}). After a stable baseline was obtained, atracurium (1.2 or 0.5 mg/kg) or histamine (200 μg) were administered as an iv bolus, and percent increase in R_{cs} was calculated. On separate days dogs were pretreated with the histamine$_1$ receptor antagonist, chlorpheniramine (0.2 mg/kg iv), with or without atropine (0.2 mg/kg iv) and ranitidine (0.75 mg/kg iv) and the experiment repeated. Histamine (200 μg) increased R_{cs} 97 ± 24% at 30 s (8 sublobar segments), whereas a second dose increased R_{cs} 77 ± 15%. Pretreatment with chlorpheniramine (0.2 mg/kg iv) totally prevented increases in R_{cs} (9 sublobar segments). Atracurium (1.2 mg/kg) increased R_{cs} to 174 ± 35% at 3 min (14 sublobar segments), whereas 0.5 mg/kg had little effect (10 sublobar segments). A second bolus of atracurium (1.2 mg/kg) increased R_{cs} to only 54 ± 14% (P < 0.01). Chlorpheniramine pretreatment (0.2 mg/kg iv) reduced the response to the initial dose of atracurium to only 26 ± 14% (10 sublobar segments). Pretreatment with a combination of atropine and chlorpheniramine (4 sublobar segments), or ranitidine and chlorpheniramine (5 sublobar segments), did not attenuate the increase in R_{cs} significantly more than chlorpheniramine pretreatment alone. We conclude that atracurium produces airway constriction in Basenji-Greyhound dogs and that release of histamine acting on histamine$_1$ receptors in the airways is important for this effect. (Key words: Antagonists, histamine: chlorpheniramine; ranitidine. Bronchoconstriction: drug effects. Neuromuscular relaxants: atracurium.)

NEUROMUSCULAR BLOCKING DRUGS possess two characteristics which can, at least theoretically, alter airway tone. They are capable of inducing release of histamine from mast cells lining the vessels into which they are injected.[1] In addition, in order to interact with receptors at the neuromuscular junction, these drugs must structurally resemble acetylcholine. Thus, it is possible that they may bind to muscarinic receptors on airway smooth muscle,[2] leading to constriction.

Both d-tubocurarine and atracurium cause release of histamine from human mast cell preparations.[3,4] Intravenously administered d-tubocurarine increases plasma histamine concentration in some patients and produces hypotension,[5] presumably due to direct relaxation effects of histamine on histamine$_1$ (H_1) and histamine$_2$ (H_2) receptors in vascular smooth muscle.[6] In contrast, histamine mediates contraction of airway smooth muscle by activation of H_1 receptors.[7] However, evidence showing a relationship between drug-induced histamine release and increases in airway tone is less than compelling.[8-10] Moreover, in studies in which the administration of histamine releasing drugs or histamine itself[11-14] produced cardiovascular effects, airway resistance was not measured, and bronchospasm was not reported as a symptom. These studies all were conducted in either normal volunteers or patients with no history of asthma. Mast cells from asthmatic patients show increased histamine releasability,[15] and airways of asthmatic patients are exquisitely sensitive to histamine.[16] Drugs stimulating release of histamine may produce significant effects on airways in such high-risk populations.

We therefore asked whether a clinically relevant dose of the neuromuscular blocking drug, atracurium, produced significant increases in airway tone and, if so, what mechanisms governed the effect in a dog model that showed both increased release of histamine from mast cells[17] and increased airway sensitivity to histamine.[18]

Materials and Methods

These studies were approved by the Animal Research Committee of The Johns Hopkins University. Eight Basenji-Greyhound (BG) dogs (weight = 18.5 ± 0.7kg) were anesthetized with intravenous (iv) sodium thiopental (17 mg/kg). Maintenance anesthesia consisted of a continuous infusion of sodium thiopental (7–10 mg·kg^{-1}·h^{-1}), with supplemental doses of fentanyl citrate (25–50 μg) administered every 10–30 min. The dogs were not paralyzed. A Harvard constant-volume ventilator (Millis, MA) was used to ventilate the lungs with room air via an endotracheal tube. Tidal volume was set at 17 ml/kg, and respiratory rate was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5%. Rectal temperature was monitored and maintained within 1° C of the initial temperature. The electrocardiogram was monitored continuously (Tektronics, Beaverton, OR). Neuromuscular blockade was evaluated by stimulation of the posterior tibial nerve (Neurotechnology, Houston, TX) and assessment of visible dorsiflexion of the animal's hind limb. Blood pressure was measured either noninvasively (Data-

scope, Paramus, NJ) every 2.5 min or *via* a 20-G percutaneous femoral arterial catheter connected to a pressure transducer. Anesthetic depth was assessed by canthal reflex, presence of spontaneous movement, breathing, heart rate, and blood pressure.

One or two fiberoptic bronchoscopes (5.5 mm OD) were visually guided through the endotracheal tube, and the tip(s) were lodged in a sublobar airway. A double-lumen catheter (5-Fr) was threaded through the suction port of the bronchoscope. Through one lumen, 5% carbon dioxide in air was delivered to the obstructed segment. A constant flow rate of 200 ml/min ($\dot{V}_{coll}$), approximating the resting ventilation to the area subtended by the bronchoscope, was maintained throughout the experiment. The other lumen of the double-lumen catheter was connected to a transducer to measure the pressure (P_b) at the tip of the bronchoscope. Collateral system resistance (R_{cs}) was determined by stopping the ventilator to allow the dog to exhale to functional residual capacity. At this point P_b reached a plateau, and the pressure in the surrounding unobstructed lung (P_{ao}) equaled zero. R_{cs} ($cmH_2O \cdot ml^{-1} \cdot s^{-1}$) was calculated as follows: $R_{cs} = (P_b - P_{ao})/\dot{V}_{coll}$.[19]

Data are presented as percent increase in R_{cs}: % R_{cs} = $(R_{cs}A-R_{cs}B)/R_{cs}B \cdot 100$, where $R_{cs}A$ is R_{cs} measured 30 s or 3 min after an iv challenge, and $R_{cs}B$ is an average of three measurements of R_{cs} just before each challenge.

At the end of the experiment, neostigmine (50 μg/kg) and atropine (25 μg/kg) were administered every 30 min until full strength had returned. The dogs were monitored continuously until they were fully awake.

EXPERIMENTAL PROTOCOL

Effect of Histamine

Repeated Doses: Four BG dogs were anesthetized, and two fiberoptic bronchoscope tips were wedged in sublobar segments (four right middle and four left middle lobes). In each sublobar segment, R_{cs} was measured every 5 min until a stable baseline was established for three consecutive readings. Histamine (200 μg) was then given as an iv bolus, and R_{cs} subsequently measured 30 s, 2, 5, and 10 min after the bolus. Thereafter, R_{cs} was measured every 5 min until it stabilized for three consecutive readings. A second dose of histamine (200 μg iv) was then administered and R_{cs} measured as described above. This dose of histamine was selected based on preliminary experiments that showed that histamine (200 μg iv) produced an increase in R_{cs} similar to that of atracurium (1.2 mg/kg) used in subsequent experiments.

Chlorpheniramine: The effect of a H_1 antagonist, chlorpheniramine, was studied in five BG dogs. Two fiberoptic bronchoscopes were inserted into four dogs (four right

middle lobes, four left middle lobes), and one bronchoscope was inserted into one dog (left middle lobe). The protocol was identical to that described above, except that chlorpheniramine (0.2 mg/kg iv) was administered between the two histamine challenges.

Effect of Atracurium

Repeated doses: Seven BG dogs (seven right middle lobes, seven left middle lobes) were studied. R_{cs} was measured every 5 min until a stable baseline was established for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered, and R_{cs} was measured 1, 2, 3, 4, 5, 10, and 15 min after the bolus. When R_{cs} returned to the original baseline, a second dose of atracurium (1.2 mg/kg iv) was administered and R_{cs} measured as described above.

To determine whether a smaller dose of atracurium increased collateral resistance, six BG dogs were studied on a separate occasion. Two fiberoptic bronchoscopes were inserted into four dogs (four right middle lobes, four left middle lobes), and one bronchoscope was inserted into two dogs (one right middle lobe, one left middle lobe). After a stable baseline R_{cs} was established, atracurium (0.5 mg/kg iv) was administered and R_{cs} measured as described above.

Chlorpheniramine: Five BG dogs were pretreated with chlorpheniramine (0.2 mg/kg iv) after the induction of anesthesia. Two bronchoscope tips were wedged in sublobar segments (five right middle lobes, five left middle lobes). R_{cs} was measured every 5 min until it stabilized for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered within 11 min of the dose of chlorpheniramine, and R_{cs} was measured.

This study was repeated using high-dose chlorpheniramine (5 mg/kg iv) in five dogs (one dog was studied twice). Two bronchoscope tips were wedged in sublobar segments (six right middle lobes, six left middle lobes).

Chlorpheniramine and Atropine: Two BG dogs were pretreated with atropine (0.2 mg/kg iv) and then chlorpheniramine (0.2 mg/kg iv) after the induction of anesthesia. The tips of two bronchoscopes were wedged in sublobar segments (two right middle lobes, two left middle lobes). R_{cs} was measured every 5 min until it stabilized for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered with 17 min of the atropine and within 13 min of the chlorpheniramine, and R_{cs} was measured.

Chlorpheniramine and Ranitidine: Three BG dogs were pretreated with chlorpheniramine (0.2 mg/kg iv) and then ranitidine (0.75 mg/kg iv) after the induction of anesthesia. Two fiberoptic bronchoscopes were inserted into each of two dogs (two right middle lobes, two left middle lobes), and one bronchoscope was inserted into

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one dog (right middle lobe). R_{cs} was measured every 5 min until it stabilized for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered within 26 min of the chlorpheniramine and within 20 min of the ranitidine, and R_{cs} was measured.

STATISTICAL ANALYSIS

Analysis of variance and Fisher multiple comparison tests were used to analyze mean differences of R_{cs} within sublobar segments, and blood pressure and heart rate responses within animals. T tests were used to analyze mean differences of R_{cs} between sublobar segments. Raw data were used for all statistical analyses. We used $P < 0.05$ to indicate statistical significance. Data are expressed as mean ± standard error.

Results

EFFECT OF HISTAMINE

Repeated Doses

Histamine (200 µg iv) increased R_{cs}, decreased systolic blood pressure, and increased heart rate (fig. 1). Baseline R_{cs} before the first dose of histamine (200 µg iv) was 0.38 ± 0.09 cmH$_2$O·ml^{-1}·s^{-1} (n = 8 sublobar segments). Histamine increased R_{cs} to 0.68 ± 0.14, a 97 ± 24% (P < 0.01) increase above baseline at 30 s (fig. 1). R_{cs} returned to baseline by 10 min. Baseline R_{cs} before the second dose of histamine was 0.37 ± 0.09 cmH$_2$O·ml^{-1}·s^{-1}, which was not significantly different from the first baseline R_{cs}. After the second dose of histamine, R_{cs} increased to 0.66 ± 0.18 cmH$_2$O·ml^{-1}·s^{-1}, a 77 ± 15% increase above the initial baseline at 30 s. R_{cs} after the second dose of histamine was not significantly different from R_{cs} after the first dose. Reductions in blood pressure and increases in heart rate were similar after the two doses of histamine (fig. 1).

Chlorpheniramine

Chlorpheniramine (0.2 mg/kg) totally prevented the histamine-induced increase in airway tone (fig. 2). Baseline R_{cs} was 0.40 ± 0.08 cmH$_2$O·ml^{-1}·s^{-1} (n = 9 sublobar segments). Histamine (200 µg iv) increased R_{cs} to 0.62 ± 0.10 cmH$_2$O·ml^{-1}·s^{-1}, or 65 ± 16% increase above baseline at 30 s (fig. 2). After the administration of chlorpheniramine, baseline R_{cs} (0.41 ± 0.07 cmH$_2$O·ml^{-1}·s^{-1}) was not significantly different from baseline R_{cs} in the absence of chlorpheniramine. In the presence of chlorpheniramine, histamine did not significantly increase R_{cs}. In the presence of chlorpheniramine, histamine decreased systolic blood pressure from 156 ± 19 mmHg to 139 ± 24 mmHg at 30 s (fig. 2). This reduction was not significantly

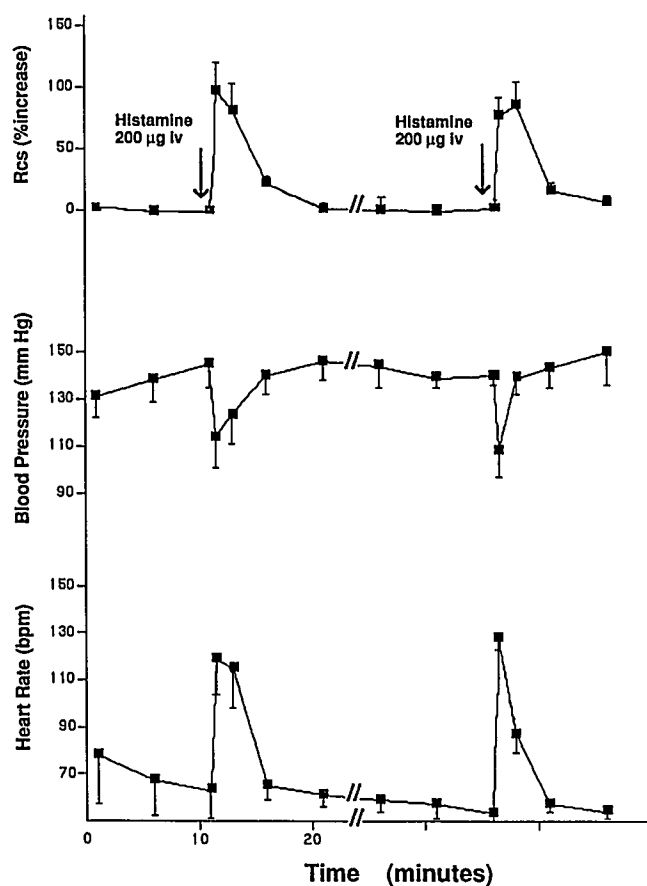FIG. 1. Airway resistance (R_{cs}), blood pressure, and heart rate in response to two sequential iv bolus doses of histamine (200 µg iv) in Basenji-Greyhound dogs. n = 8 sublobar segments.

different from the reduction in blood pressure in the absence of chlorpheniramine. In the presence of chlorpheniramine, histamine increased heart rate from 74 ± 9 beats per min to 109 ± 14 beats per min at 30 s. Maximum heart rate was significantly less in the presence of chlorpheniramine (P < 0.05).

EFFECT OF ATRACURIUM

Repeated Doses

Atracurium produced significant effects on both airways and the cardiovascular system. Atracurium (1.2 mg/kg) produced an increase in R_{cs}, a decrease in systolic blood pressure, and an increase in heart rate (fig. 3). Before the first dose of atracurium (1.2 mg/kg), baseline R_{cs} was 0.23 ± 0.04 cmH$_2$O·ml^{-1}·s^{-1} (n = 14 sublobar segments). Peak response to atracurium occurred 3 min after the bolus (fig. 3), at which time R_{cs} increased to 0.67 ± 0.16 cmH$_2$O·ml^{-1}·s^{-1}, or 174 ± 35% above the baseline. By 10 min, R_{cs} had returned to baseline. Before the second dose of atracurium, baseline R_{cs} was 0.22 ± 0.04
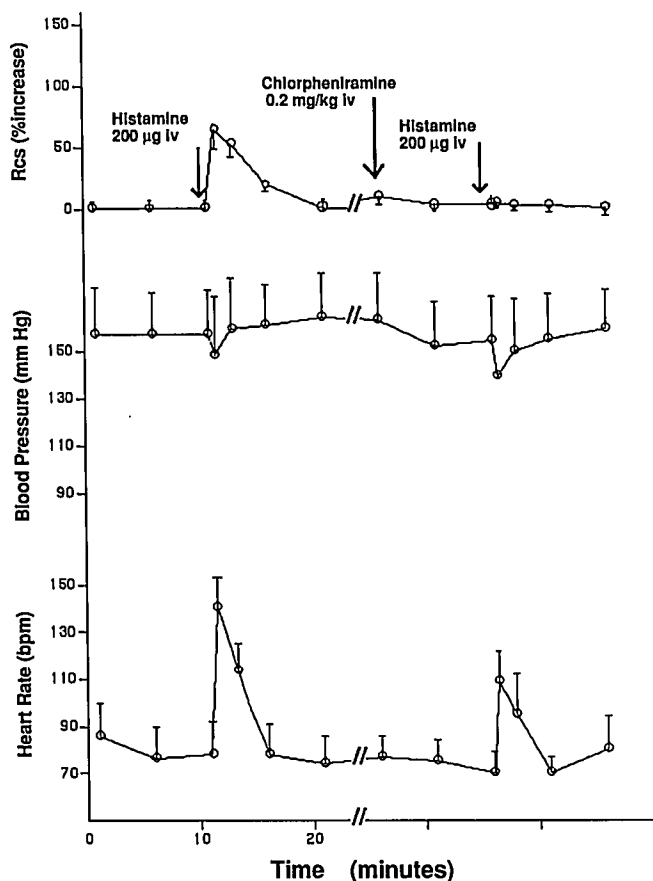
FIG. 2. Airway resistance (R_{cs}), blood pressure, and heart rate in response to two sequential iv bolus doses of histamine (200 μg iv) in the presence and absence of chlorpheniramine (0.2 mg/kg iv) in Basenji-Greyhound dogs. n = 9 sublobar segments.

$cmH_2O \cdot ml^{-1} \cdot s^{-1}$, which was not significantly different from the baseline before the first dose. A second dose of atracurium, administered 19–43 min after the first dose, increased R_{cs} to only 0.38 ± 0.09 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$, or 54 ± 14% above baseline at 3 min. Thus, peak R_{cs} was significantly less than peak R_{cs} following the first dose of atracurium ($P < 0.01$).

Systolic blood pressure before the first dose of atracurium was 142 ± 5 mmHg and decreased to 81 ± 8 mmHg at 3 min (fig. 3). Before the second dose of atracurium, systolic blood pressure was 145 ± 7 mmHg and decreased to 112 ± 10 mmHg after the second dose of atracurium. The lowest systolic blood pressure was significantly different between the first and second doses ($P < 0.01$). Atracurium increased heart rate from 101 ± 5 beats per min to 155 ± 7 beats per min after the first dose (fig. 3) and from 134 ± 7 beats per min to 143 ± 11 beats per min after the second dose. The peak heart rate after the second dose of atracurium was not significantly different from the peak heart rate after the first dose.

Varying Doses

Atracurium (0.5 mg/kg) did not significantly increase R_{cs}: R_{cs} was 0.24 ± 0.05 and 0.25 ± 0.05 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$ (n = 10 sublobar segments) before and 3 min after atracurium, respectively ($P = 0.48$).

Chlorpheniramine

Chlorpheniramine significantly attenuated but did not abolish the increase in R_{cs}. Baseline R_{cs} in dogs pretreated with low-dose chlorpheniramine (0.2 mg/kg) was 0.37 ± 0.08 $cmH_2O \cdot ml^{-1} \cdot s \cdot ^{-1}$ (n = 10 sublobar segments). Atracurium given within 11 min of the chlorpheniramine dose produced a significant increase in R_{cs} (fig. 3) ($P = 0.0001$). In the presence of chlorpheniramine, atracurium increased peak R_{cs} to 0.52 ± 0.13 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$ or only 26 ± 14% above baseline at 3 min. Baseline systolic blood pressure decreased from 144
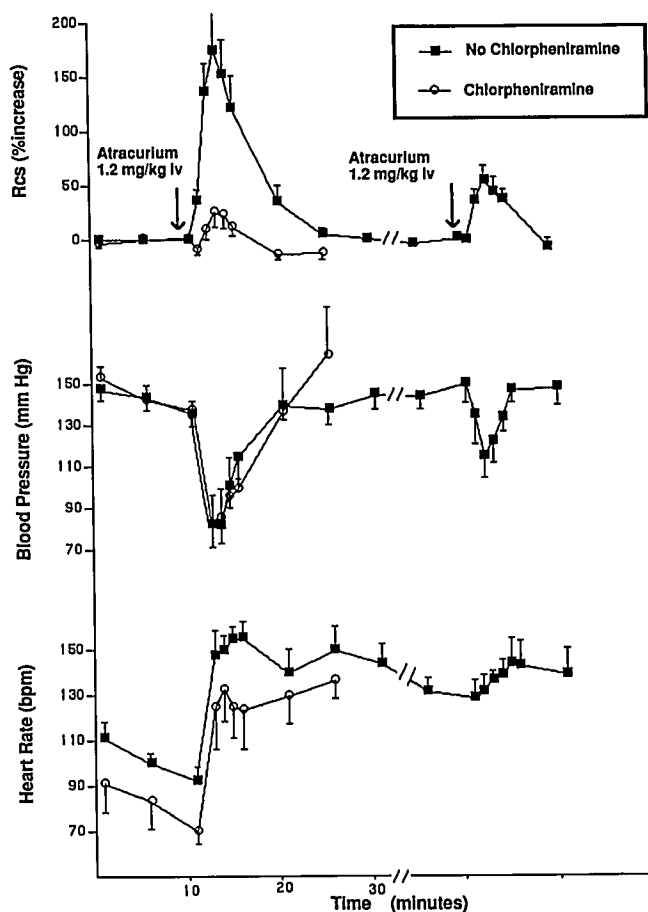

FIG. 3. Airway resistance (R_{cs}), blood pressure, and heart rate in response to atracurium (1.2 mg/kg iv bolus) with and without chlorpheniramine (0.2 mg/kg iv) pretreatment in Basenji-Greyhound dogs. n = 14 sublobar segments without chlorpheniramine; n = 10 sublobar segments with chlorpheniramine.

$\pm$ 4 mmHg to 82 $\pm$ 14 mmHg postchallenge (fig. 3). Baseline heart rate increased from 81 $\pm$ 10 beats per min to 132 $\pm$ 14 beats per min postchallenge (fig. 3).

In animals pretreated with high-dose chlorpheniramine (5 mg/kg), atracurium (1.2 mg/kg) did not significantly increase R_{cs} during the 10-min period of observation (n = 12 sublobar segments). Baseline R_{cs} following pretreatment with chlorpheniramine (5 mg/kg) was 0.17 $\pm$ 0.03 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$ (table 1). Atracurium (1.2 mg/kg) did not significantly increase R_{cs}. In fact, a small reduction in R_{cs} to 0.14 $\pm$ 0.03 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$ was observed (P = 0.023).

Chlorpheniramine and Atropine

The combination of atropine and chlorpheniramine was no more protective than chlorpheniramine alone. Baseline R_{cs} after pretreatment with both chlorpheniramine (0.2 mg/kg iv) and atropine (0.2 mg/kg iv) was 0.36 $\pm$ 0.11 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$ (n = 4 sublobar segments) (table 1). R_{cs} increased to 0.53 $\pm$ 0.17 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$, a 45 $\pm$ 12% increase, after the administration of atracurium. Peak R_{cs} was not significantly different from peak R_{cs} (0.52 $\pm$ 0.13 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$) following pretreatment with chlorpheniramine alone (P = 0.98). Baseline systolic blood pressure after chlorpheniramine and atropine pretreatment was 151 $\pm$ 1 mmHg and decreased to 44 $\pm$ 6 postchallenge (P < 0.01). Baseline heart rate after chlorpheniramine and atropine pretreatment was 169 $\pm$ 5 beats per min, which did not significantly change after administration of atracurium.

Chlorpheniramine and Ranitidine

The addition of ranitidine did not increase the protection afforded by chlorpheniramine. Baseline R_{cs} in dogs pretreated with chlorpheniramine (0.2 mg/kg iv) and ranitidine concurrently (0.75 mg/kg iv) was 0.32 $\pm$ 0.08 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$ (n = 5 sublobar segments) (table 1).

R_{cs} increased to 0.46 $\pm$ 0.12 $cmH_2O \cdot ml^{-1} \cdot s^{-1}$, 47 $\pm$ 29% above baseline, 3 min after atracurium (table 1). Peak R_{cs} was not significantly different from peak R_{cs} following pretreatment with chlorpheniramine alone (P = 0.74). Systolic blood pressure, after pretreatment with chlorpheniramine and ranitidine, was 143 $\pm$ 4 mmHg and did not decrease after atracurium challenge. Baseline heart rate after chlorpheniramine and ranitidine was 95 $\pm$ 21 beats per min, which did not significantly change after administration of atracurium.

Discussion

The present study demonstrates that atracurium produces significant effects on the airways as well as on the cardiovascular system. The airway effects are short-lived, are dose-related, are qualitatively similar to an iv bolus of histamine, and are markedly attenuated by pretreatment with a H_1 receptor antagonist.

Crago et al.,[10] Simpson et al.,[9] and Gerbershagan and Bergman[8] failed to find significant increases in airway tone after administration of d-tubocurarine to humans with normal lung function. However, Crago et al.[10] did find greater increases in airway resistance in subjects with preexisting lung disease paralyzed with d-tubocurarine, than with pancuronium, but did not follow up this observation with histamine receptor antagonist studies.

We are aware of only one study in humans that examined changes in airway tone after atracurium.[9] Simpson et al.[9] found a significant decrease in specific airways conductance at only one time point, 6 min after administration of a 0.5-mg/kg dose to humans. Our results differ from those of Simpson et al.[9] in that the peak effect on airways occurred 3 min after administration of an even higher dose of drug. A maximal effect at 3 min, not 6 min, agrees with the study of Moss et al.,[5] who showed that, for d-tubocurarine, maximal plasma histamine concentrations were attained at 2 min and that by 5 min,

TABLE 1. Peripheral Airway Resistance (R_{cs}) Before and After Histamine and Atracurium

Treatment	Baseline	Peak R_{cs}	Sublobar Segments
Histamine 200-μg iv bolus			
First dose	0.38 $\pm$ 0.09	0.68 $\pm$ 0.14	n = 8
Second dose	0.37 $\pm$ 0.09	0.66 $\pm$ 0.18	n = 8
Chlorpheniramine 0.2-mg/kg pretreatment	0.41 $\pm$ 0.07	0.41 $\pm$ 0.07	n = 9
Atracurium 1.2-mg/kg iv bolus			
First dose	0.23 $\pm$ 0.04	0.67 $\pm$ 0.16	n = 14
Second dose	0.22 $\pm$ 0.04	0.38 $\pm$ 0.09	n = 14
Chlorpheniramine 0.2-mg/kg pretreatment	0.37 $\pm$ 0.08	0.52 $\pm$ 0.13	n = 10
Chlorpheniramine 5-mg/kg pretreatment	0.17 $\pm$ 0.03	0.17 $\pm$ 0.03	n = 12
Chlorpheniramine 0.2-mg/kg and atropine 0.2-mg/kg pretreatment	0.36 $\pm$ 0.11	0.53 $\pm$ 0.17	n = 14
Chlorpheniramine 0.2-mg/kg and ranitidine 0.75-mg/kg pretreatment	0.32 $\pm$ 0.08	0.46 $\pm$ 0.12	n = 5
Atracurium 0.5-mg/kg iv bolus			
One dose	0.24 $\pm$ 0.05	0.25 $\pm$ 0.05	n = 10

histamine concentrations had returned to control values. Clinically significant effects on both the airways and the cardiovascular system were not seen in our study with the lower dose (0.5 mg/kg) of atracurium. This agrees with a study in humans[20] that showed that significant increases in heart rate and decreases in mean arterial blood pressure occurred after a bolus of a higher dose than 0.5 mg/kg of atracurium. A steep dose–response relationship for histamine release by atracurium from human mast cells has also been demonstrated.[3,4]

Plasma histamine concentrations were not measured in this study because it was unclear to us at which site they should be measured. Measured plasma levels of histamine only roughly reflect histamine release from tissue but do not presumably account for the large amount of histamine metabolized or taken up within various tissue beds. Instead, we elected to inject into the systemic circulation a bolus dose of histamine that produced a similar airway constrictor response to atracurium 1.2 mg/kg. Two differences were seen between histamine and atracurium. Atracurium induced peak effects on airways at 3 min, whereas peak effects of histamine were seen at 30 s. Moreover, the airways exhibited reduced responsiveness to a second dose of atracurium but not to histamine, presumably reflecting depleted histamine stores in the mast cells, not rapid desensitization of the airways to circulating histamine.

Both vascular and airway smooth muscle contain H_1 and H_2 receptors. Histamine induces dilatation of resistance vessels by stimulation of both H_1 and H_2 receptors. H_1 receptors are believed to mediate the immediate response, whereas H_2 receptors are believed to mediate the more sustained response.[21] In contrast, histamine produces constriction of airway smooth muscle of many species including the human and the dog, mediated by H_1 receptors.[22] However, in the presence of H_1 blockade histamine can induce bronchodilation mediated by H_2 receptors.[22] Our results are consistent with these theories. A combination of H_1 and H_2 receptor blockade significantly attenuated the cardiovascular effects of atracurium. Moreover, H_1 receptor blockade totally abolished histamine-induced airway constriction and markedly attenuated atracurium-induced airway constriction. It is unlikely that the small residual constriction provoked by atracurium in the presence of H_1 receptor blockade was due to stimulation of muscarinic cholinergic receptors,[2] since atropine in concentrations known to block airway muscarinic receptors[23] failed to modify this response. A combination of H_1 and H_2 receptor blockade also failed to abolish the small residual constriction provoked by atracurium. It is possible that H_2 receptor–induced dilatation is not important in this model. It is also possible that H_2 antagonists could have concurrently increased histamine release from mast cells, since histamine acting

via H_2 receptors has been shown to inhibit histamine release from basophils.[24] A more likely possibility is that the small residual constriction reflects the presence in the airways of other bronchoactive inflammatory mediators released along with histamine.

One additional explanation for the residual airway constriction is prejunctional activity of atracurium. One study in dogs showed that atracurium increased total pulmonary resistance during vagal stimulation.[25] The authors hypothesized that this could be due to blockade of prejunctional muscarinic receptors (M2) that inhibit vagally mediated increases in pulmonary resistance.

In this study, we assessed the effects of atracurium on peripheral airway resistance. We suspected that if atracurium released histamine, then changes in airway resistance would be most easily detected in the lung periphery, the predominant site of histamine-induced airway constriction in the dog.[26] Peripheral airway caliber was determined by assessing changes in R_{cs}. In the past, pathways for collateral flow were believed to be comprised of pores of Kohn, bronchoalveolar channels of Lambert, and interbronchiolar channels of Martin.[27,28] Recent evidence, however, has demonstrated that the predominant pathway for collateral flow is through interbronchiolar channels of Martin, so that R_{cs} primarily reflects resistance at the level of the alveolar duct.[19] In addition, collateral system responses are very similar to those of other normal small airways.[29,30] Thus, it appears likely that atracurium-induced changes in R_{cs} in this study truly reflect constriction of peripheral airways.

In summary, atracurium constricts peripheral airways in doses that produce significant cardiovascular effects. Release of histamine acting on H_1 receptors is important for this effect. Our study suggests that airway constrictor effects of atracurium can largely be prevented in high-risk populations by using low drug doses, divided doses, and H_1 receptor antagonists.

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