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Research Article

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Effects of Antihistamines on the Lung Vascular Response to Histamine in Unanesthetized Sheep

DIPHENHYDRAMINE PREVENTION OF PULMONARY EDEMA AND INCREASED PERMEABILITY

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ABSTRACT To see whether antihistamines could prevent and reverse histamine-induced pulmonary edema and increased lung vascular permeability, we compared the effects of a 4-h intravenous infusion of 4 $\mu\text{g/kg}$ per min histamine phosphate on pulmonary hemodynamics, lung lymph flow, lymph and plasma protein content, arterial blood gases, hematocrit, and lung water with the effects of an identical histamine infusion given during an infusion of diphenhydramine or metiamide on the same variables in unanesthetized sheep. Histamine caused lymph flow to increase from 6.0 ± 0.5 to 27.0 ± 5.5 (SEM) ml/h ($P < 0.05$), lymph:plasma globulin concentration ratio to increase from 0.62 ± 0.01 to 0.67 ± 0.02 ($P < 0.05$), left atrial pressure to fall from 1 ± 1 to -3 ± 1 cm H_2O ($P < 0.05$), and lung lymph clearance of eight protein fractions ranging from 36 to 96 Å molecular radius to increase significantly. Histamine also caused increases in lung water, pulmonary vascular resistance, arterial Pco_2 , pH, and hematocrit, and decreases in cardiac output and arterial Po_2 . Diphenhydramine (3 mg/kg before histamine followed by 1.5 mg/kg per h intravenous infusion) completely prevented the histamine effect on hematocrit, lung lymph flow, lymph protein clearance, and lung water content, and reduced histamine effects on arterial blood gases and pH. 6 mg/kg diphenhydramine given at the peak histamine response caused lymph flow and lymph:plasma protein concentration ratios to fall. Metiamide (10 mg/

kg per h) did not affect the histamine lymph response. We conclude that diphenhydramine can prevent histamine-induced pulmonary edema and can prevent and reverse increased lung vascular permeability caused by histamine, and that histamine effects on lung vascular permeability are H_1 actions.

INTRODUCTION

We showed previously that histamine infusions in unanesthetized sheep caused pulmonary edema and increased vascular permeability as reflected in measurements of lung lymph (1). We have now measured the effects of H_1 and H_2 antihistamines (diphenhydramine and metiamide) on the histamine response in the same animal preparation. Diphenhydramine prevented pulmonary edema and prevented increased lung vascular permeability due to histamine. Diphenhydramine given during the increased permeability histamine response largely reversed that change. Metiamide did not affect the permeability response. We conclude that the effects of histamine on pulmonary vascular permeability and lung water content are H_1 receptor actions and that classical antihistamines may be useful therapeutically in some forms of pulmonary edema if histamine is an important mediator.

METHODS

We made experiments in 25 young sheep weighing from 30 to 45 kg.

Description of the preparation

We used an unanesthetized, chronic sheep preparation described previously (1-4). Each animal was prepared by a series of three staged thoracotomies during which non-pulmonary contributions to a large lymph node in the posterior mediastinum (caudal mediastinal node) were resected;

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a stainless steel clip was placed at the posterior border of the left atrium, catheters were placed through neck vessels in the superior vena cava and thoracic aorta, and a small cannula was placed in the efferent duct from the caudal mediastinal node. We have shown earlier that lymph collected from sheep prepared this way is mostly from the lung since the flow does not increase when systemic venous pressure is increased, but does increase when left atrial pressure is elevated (2, 4). We made experiments without anesthesia 4–7 days after the last operation after the animals had recovered and lymph flow was stable and lymph was free of blood.

Experimental protocols

General. Before beginning a series of experiments, we located the left atrial clip fluoroscopically with the sheep standing in a special experimental cage, marked this level on the skin, and used the mark as the 0 reference for all pressures. During each experiment, the animal stood unanesthetized in the cage with free access to food and water. Throughout each experiment we recorded pulmonary arterial, left atrial, and aortic pressures continuously using miniature strain gauges (Micron Instruments, Inc., Los Angeles, Calif.) and an electronic recorder (Hewlett-Packard Co., Palo Alto, Calif.). We measured lung lymph flow each 15 min by recording the volume drained into a graduated tube fixed to the animal's side, and we measured protein concentrations in lymph samples pooled each 30 min and in peripheral blood plasma drawn each hour.

Diphenhydramine given before histamine (prevention studies). To test the ability of diphenhydramine to prevent the histamine response, we did nine pairs of experiments in five sheep. A pair of experiments consisted of one infusion of histamine alone and one infusion of diphenhydramine plus histamine done on consecutive days. We varied the order of the studies to avoid bias. In five pairs of studies, diphenhydramine plus histamine was infused first and in four pairs of studies the order was reversed. We infused histamine exactly as described earlier (1). After 2 h of base-line observation of vascular pressures, lung lymph flow, and lymph and plasma protein concentrations, we infused 4 μ g/kg per min histamine phosphate (Eli Lilly and Company, Indianapolis, Ind.) through a vena caval catheter for 4 h with a constant rate infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.). The diphenhydramine plus histamine experiments were done exactly the same way except that 15 min before beginning the histamine infusion, we injected 3 mg/kg diphenhydramine hydrochloride (Parke, Davis & Company, Detroit, Mich.) intravenously and began an intravenous infusion of 1.5 mg/kg per h diphenhydramine which was continued for the duration of the experiment.

Diphenhydramine given after histamine (reversal studies). To see whether diphenhydramine could reverse the histamine effect once it was established, we infused the drug intravenously at the height of the histamine response 16 times in six sheep. Histamine infusions were done exactly as described above. After 2 h of base-line observation of vascular pressures, lymph flow, and lymph and plasma protein concentrations, we began an intravenous infusion of 4 μ g/kg per min histamine phosphate. After lymph flow reached a peak we infused 6 mg/kg diphenhydramine hydrochloride intravenously over 30–60 min, and continued the histamine infusion for at least 4 h.

Metiamide and histamine. To see whether the H_2 anti-histamine, metiamide, could prevent the histamine response,

we did six pairs of experiments in four sheep. A pair of experiments consisted of one infusion of histamine alone and one infusion of metiamide (Smith Kline & French Laboratories, Philadelphia, Pa.) plus histamine done on consecutive days. We varied the order of the studies. We infused histamine phosphate intravenously at 4 μ g/kg per min exactly as described above for the diphenhydramine infusion. The metiamide plus histamine studies were done the same way except that 30 min before beginning the histamine infusion, we started an intravenous infusion of 10 mg/kg per h metiamide and continued the metiamide infusion throughout the 4-h histamine infusion. We made an aqueous stock solution of 1.0 M metiamide by dissolving it in 1.0 N HCl, adjusting the pH with 0.1 NaOH and diluting with distilled water. The pH of the stock solution was 6.0 and this was diluted 20-fold with 0.89% NaCl solution for infusion.

Other methods

Protein analyses. We measured total protein concentrations in lymph and blood plasma with an automated system (AutoAnalyzer, Technicon Instruments Corp., Tarrytown, N. Y.), by a modified biuret method (5); duplicate determinations differed by less than 5%. We separated protein fractions in steady-state base line and steady-state experimental lymph and blood plasma samples by polyacrylamide gradient gel electrophoresis using 4–30% gradient gel slabs (Pharmacia Fine Chemicals, Inc., Piscataway, N. J.) and Tris-barbital buffer at pH 8.0 and ionic strength 0.06. We performed electrophoresis for 16.5 h at 125 V constant voltage, stained with 0.5% Ponceau S in 7.5% TCA, destained electrophoretically in 7% acetic acid, and scanned the gels spectrophotometrically at 510 nm. With the measured total protein concentrations we calculated concentrations of each of eight protein fractions consistently identified in plasma and lymph samples. To estimate effective molecular radius for each of the eight fractions, we ran gel slabs with both lymph and plasma samples and five proteins of known molecular weight and free diffusion coefficient. With the Einstein-Stokes equation (6), we calculated the radius for each of the known proteins and plotted those values as a function of migration distance. We then estimated molecular radius of the eight plasma and lymph protein fractions from this standard curve and the location of lymph and plasma protein fractions (3).

Indicator dilution studies. We measured cardiac output and extravascular water during steady-state base-line and experimental periods 10 times in four sheep receiving histamine alone and 21 times in seven sheep receiving diphenhydramine plus histamine according to the protocol described above under "Prevention studies." Measurements were made by indicator dilution techniques, with both [51 Cr]-erythrocytes and [125 I]-albumin as intravascular indicators to avoid errors due to erythrocyte-plasma transit time differences (7, 8). Each animal's erythrocytes were labeled by incubating a blood sample for 1 h with [51 Cr]sodium chromate at room temperature and washing the cells three times with 0.89% NaCl solution. For each study we injected a mixture of 10 μ Ci [125 I]albumin, 10 μ Ci [51 Cr]erythrocytes, and 30 μ Ci [3 H]water as a bolus through the superior vena caval catheter and took arterial blood samples at 1.0-s intervals by allowing blood to flow from the aortic catheter into heparinized tubes on a precisely timed rotating disk collector. We measured radioactivity in 0.5-ml portions of each arterial blood sample and of the injected mixture diluted 1/51 in the animals' blood drawn before the study. We measured

^{51}Cr and ^{125}I activity in a gamma spectrometer (Auto Gamma model 3002, Packard Instrument Co., Inc., Downers Grove, Ill.) and ^3H activity in a liquid scintillation spectrometer (Tri-Carb model 4312, Packard Instrument Co., Inc.) after ethanol precipitation of the proteins. We plotted radioactivity injected on a log scale against time after injection on a linear scale, extrapolated the downslopes linearly, and calculated cardiac output as the inverse of the area under the ^{51}Cr curve. If curve areas for other indicators differed from that of ^{51}Cr by more than 10%, we discarded the study. We calculated mean transit times by the method of Chinard et al. (9) and extravascular water volume by the formulas of Goresky et al. (8) with hematocrit measured at the time of each study and assuming the fractional water content of whole blood equal to 0.84 and the fractional water content of plasma equal to 0.92 (2).

Postmortem lung water measurements. We killed 21 sheep, all prepared exactly as described above under "Experimental preparation" and measured postmortem extravascular lung water content. 7 animals were killed under base-line conditions, seven were killed at the end of a 4-h histamine infusion (as described under "Experimental protocols"), and seven were killed at the end of a 4-h infusion of histamine and diphenhydramine (as described under "Experimental protocols-prevention studies").

A sample of each sheep's erythrocytes was labeled with [^{51}Cr]sodium chromate for 1 h at room temperature and washed three times with 0.89% NaCl solution. We injected these cells ($25\ \mu\text{Ci}\ ^{51}\text{Cr}$) 15 min before killing the animal. The sheep was anesthetized with intravenous sodium Pentothal, put supine on a table, a cuffed endotracheal tube was inserted, and the lungs were inflated to 25 cm H_2O pressure with air. We then split the sternum, cross-clamped both lung hila, drew a sample of blood from the heart, and excised the lungs. The time from anesthesia to clamping the hila did not exceed 5 min. We homogenized the lungs in a blender (John Oster Mfg. Co., Milwaukee, Wisc.), mea-

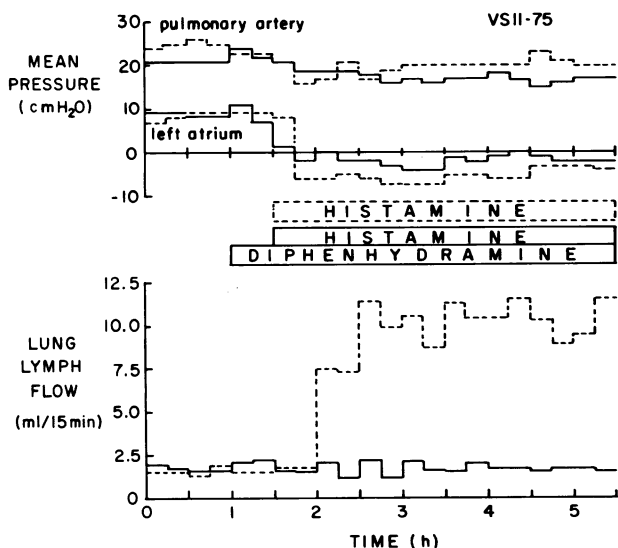


FIGURE 1 Mean pulmonary arterial and left atrial pressures and lung lymph flow during an infusion of histamine alone and during an infusion of diphenhydramine and histamine (see Methods for specific protocols). The experiments were done on consecutive days in the same animal; the diphenhydramine plus histamine study was done first.

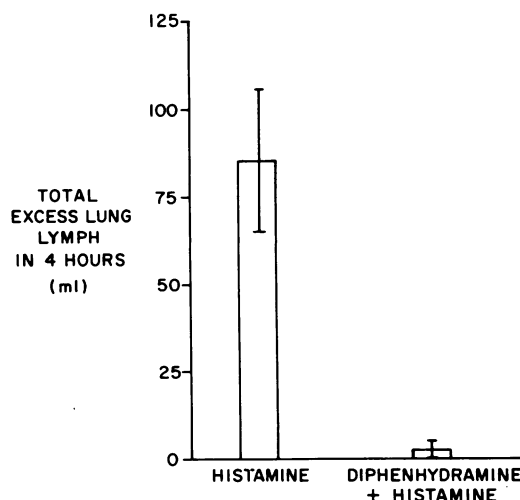


FIGURE 2 Total volume of lung lymph in excess of steady-state base-line lymph flow collected during 4-h infusions of histamine alone and during 4-h infusions of diphenhydramine and histamine (see Methods for specific protocols). Values are mean \pm SEM for nine studies in five sheep in each case.

sured ^{51}Cr activity in samples of homogenate and blood drawn at death in a gamma spectrometer (Packard Instrument Co., Inc.) and measured fractional water content of samples of homogenate and blood by drying to constant weight in a 70°C oven. Assuming water content and radioactivity concentrations in the blood drawn at death equal to those of residual lung blood, we calculated extravascular lung water by the formulas of Pearce et al. (10). We expressed these values as a ratio of quantity of extravascular water to dry weight of bloodless lung.

Blood gas measurements. We measured PO_2 , PCO_2 , and pH in samples of arterial blood collected anaerobically during steady-state base-line and experimental periods with a blood gas analyzer (model 127, Instrumentation Laboratories, Inc., Lexington, Mass.). We made these measurements 15 times in eight sheep receiving histamine alone and 16 times in six sheep receiving diphenhydramine plus histamine.

Statistics. We tested significance of differences between steady-state base-line and experimental measurements made in the same animals in the same experiments using a paired t test and between measurements made in different animals using a t test for independent groups (11). We considered a P value less than 0.05 significant.

RESULTS

Diphenhydramine prevention studies. Fig. 1 shows average pulmonary arterial and left atrial pressures and lung lymph flow from two experiments done on consecutive days in the same animal, one experiment with histamine alone and one with diphenhydramine and histamine. As we have reported before (1), histamine infusion causes left atrial pressure to fall and lymph flow to increase markedly. The responses reach a plateau 60–90 min after the histamine infusion is begun and the plateau lasts for the duration of the infusion. When a diphenhydramine infusion was begun before histamine

TABLE I
Summary of Steady-State Data for Histamine and Diphenhydramine Plus Histamine Experiments

Sheep no.	Body wt.	Sex	Conditions	No. of studies	Ppa*	Pla*	Q _{lym} †	Protein concentration, g/100 ml					
								Lymph		Plasma		Lymph/plasma	
								Alb‡	Glob‡	Alb‡	Glob‡	Alb‡	Glob‡
	Kg				cm H ₂ O		ml/h						
VS31-74	44	M	Base line	2	18	4	2.8	2.75	2.66	3.05	3.93	0.90	0.68
			Histamine	1	13	-2	8.3	2.68	2.15	2.98	2.86	0.90	0.75
			Diphenhydramine + histamine	1	16	6	2.7	3.09	2.45	3.44	3.78	0.90	0.65
VS1-75	44	M	Base line	8	14	0	5.1	2.18	2.36	2.64	3.84	0.83	0.61
			Histamine	4	13	-3	15.1	1.99	2.36	2.40	3.54	0.83	0.66
			Diphenhydramine + histamine	4	12	0	6.4	2.28	2.28	2.78	3.76	0.82	0.60
VS10-75	38	M	Base line	4	24	-1	8.6	1.72	2.20	2.29	3.86	0.75	0.57
			Histamine	2	19	-1	40.9	1.72	2.12	1.96	3.52	0.87	0.60
			Diphenhydramine + histamine	2	21	-4	9.0	1.86	2.02	2.44	3.52	0.77	0.58
VS11-75	43	M	Base line	2	22	8	6.4	1.97	2.68	2.26	4.40	0.86	0.61
			Histamine	1	19	-4	41.3	2.38	2.82	2.74	3.80	0.87	0.74
			Diphenhydramine + histamine	1	17	-2	6.8	1.83	3.14	2.10	4.57	0.87	0.69
VS13-75	34	M	Base line	2	19	1	6.5	1.82	3.44	2.88	4.95	0.80	0.70
			Histamine	1	12	-6	52.0	2.33	2.65	2.54	3.48	0.92	0.67
			Diphenhydramine + histamine	1	16	-7	9.2	2.00	2.77	2.14	4.75	0.93	0.58
Mean	41		Base line	18	18	1	6.0	2.07	2.52	4.05	0.82	0.82	0.62
±SEM	±4				±1	±1	±0.5	±0.09	±0.11	±0.09	±0.11	±0.02	±0.01
			Histamine	9	15	-3	27.0	2.10	2.37	2.42	3.54	0.86	0.67
					±1	±1	±5.5	±0.14	±0.12	±0.13	±0.12	±0.03	±0.02
			Diphenhydramine + histamine	9	16	-2	6.9	2.19	2.39	2.63	3.91	0.83	0.61
					±1	±1	±1.0	±0.14	±0.16	±0.15	±0.19	±0.03	±0.02

Values are means for all experiments done in each animal, but statistical analysis was done using paired base-line and experimental values for each experiment. In each experiment, base-line values were averaged over the 2-h base-line period and experimental values were averaged over the last 60 min of histamine infusion (see Methods).

* Ppa and Pla are pulmonary arterial and left atrial pressures, respectively, referred to the posterior border of the left atrium.

† Q_{lym} is lung lymph flow.

‡ Alb is albumin, glob is the sum of all serum or lymph proteins except albumin.

|| Significantly different from base line ($P < 0.05$).

and continued throughout the histamine infusion, the lymph flow response to histamine was completely abolished. With diphenhydramine and histamine, left atrial pressure declined less and pulmonary artery pressure fell more than with histamine alone in the experiments illustrated. The degree to which diphenhydramine prevented the lymph flow response to histamine is illustrated in Fig. 2 where the total volume of lymph in excess of base line collected during the 4-h histamine infusions with and without diphenhydramine is shown. Diphenhydramine completely prevented the lymph flow increase.

Table I summarizes steady-state data from nine pairs of experiments like the ones illustrated in Fig. 1. The responses to histamine were similar to those we reported earlier (1). Histamine caused left atrial pressure to fall and lung lymph flow to increase an average of approximately fourfold from base line. Lymph protein concen-

trations did not change with histamine in spite of the large increase in lymph flow; the lymph:plasma ratio for globulin increased. Diphenhydramine completely prevented the increase in lymph flow due to histamine. The only variable which changed significantly from base line during diphenhydramine plus histamine infusion was pulmonary artery pressure which fell slightly.

Fig. 3 shows steady-state lymph protein clearance (lymph flow \times lymph:plasma concentration ratio) for eight protein fractions as a function of Einstein-Stokes molecular radius during base line, histamine, and diphenhydramine plus histamine infusions. As reported earlier, histamine caused clearance for all of the proteins to increase markedly. Diphenhydramine prevented this increase for all of the fractions.

Steady-state measurements of lung water, hemodynamics, blood gases, and hematocrit during base line, histamine infusion, and diphenhydramine plus histamine

infusion are summarized in Table II. Histamine caused cardiac output to fall, pulmonary vascular resistance to increase, P_{aO_2} to fall, P_{aCO_2} to rise slightly, arterial blood pH to increase, and hematocrit to rise. Histamine caused pulmonary edema, reflected in an increase in extravascular lung water content measured both by indicator dilution and postmortem methods. Diphenhydramine prevented the increase in lung water measured by both methods. Diphenhydramine also prevented the increase in hematocrit and reduced the arterial pH and P_{aO_2} changes, but did not affect the fall in cardiac output, increase in pulmonary vascular resistance, or rise in P_{aCO_2} .

Diphenhydramine reversal studies. Fig. 4 shows an experiment in which diphenhydramine was given after the histamine response was established. When diphenhydramine was infused, left atrial pressure rose, pulmonary artery pressure fell slightly, and lung lymph flow fell

precipitously. The diphenhydramine effects dissipated over 4 h.

Fig. 5 summarizes the effects of diphenhydramine given during the histamine response 16 times in six sheep. The figure shows average pulmonary vascular pressures, lung lymph flow, and lymph:plasma total protein concentration ratios during base line, at the peak of the lymph flow response before giving diphenhydramine, and at the maximum diphenhydramine effect. Diphenhydramine caused significant decreases in pulmonary artery pressure, increases in left atrial pressure, decreases in lymph flow, and decreases in lymph:plasma protein ratios.

Metiamide prevention studies. Fig. 6 compares the effects of histamine alone and histamine given during metiamide infusion on lung vascular pressures, lung lymph flow, and lymph:plasma protein concentration ratios. In the presence of metiamide, histamine caused

TABLE II
Summary of Hemodynamic, Lung Water, Blood Gas, and Hematocrit Measurements during Steady-State Base-Line, Histamine Infusion, and Diphenhydramine Plus Histamine Infusion

	Base line	Histamine	Diphenhydramine +histamine
Postmortem lung water extravascular water/dry wt. bloodless lung	4.36±0.06 (7/7)	5.24±0.10* (7/7)	4.38±0.19‡ (7/7)
Indicator dilution extravascular water, ml/kg	5.1±0.1 (31/11)	7.0±0.3* (10/4)	4.6±0.2‡ (21/7)
Cardiac output, ml/min × kg	147±5 (31/11)	127±4* (10/4)	124±6* (21/7)
Pulmonary vascular resistance, cm H ₂ O/ml per min × kg	0.109±0.006 (31/11)	0.136±0.009* (10/4)	0.141±0.009* (21/7)
Arterial blood P_{O_2} , torr	92±2 (31/14)	63±3* (15/8)	88±3*‡ (16/6)
Arterial blood P_{CO_2} , torr	39±1 (28/14)	40±1* (15/8)	44±2* (13/6)
Arterial blood, pH	7.47±0.01 (24/14)	7.63±0.01* (15/8)	7.49±0.04*‡ (9/6)
Arterial blood hematocrit	0.27±0.01 (36/15)	0.33±0.01* (15/8)	0.27±0.01‡ (21/7)

All values are Mean±SEM. Numbers in parentheses are *n* observations/*n* animals. Base-line values were obtained during the stable period before any intervention, histamine measurements were made at the end of a 4-h intravenous histamine infusion (see Methods), and diphenhydramine + histamine measurements were made at the end of a 4-h intravenous histamine infusion given during diphenhydramine infusion (see Methods). Except for postmortem measurements, statistics were done using paired base-line and experimental observations from each experiment (paired *t* test). All base-line values are averaged in the table for convenience.

* Significantly different from base line ($P < 0.05$).

‡ Significantly different from steady-state histamine values ($P < 0.05$, unpaired *t* test).

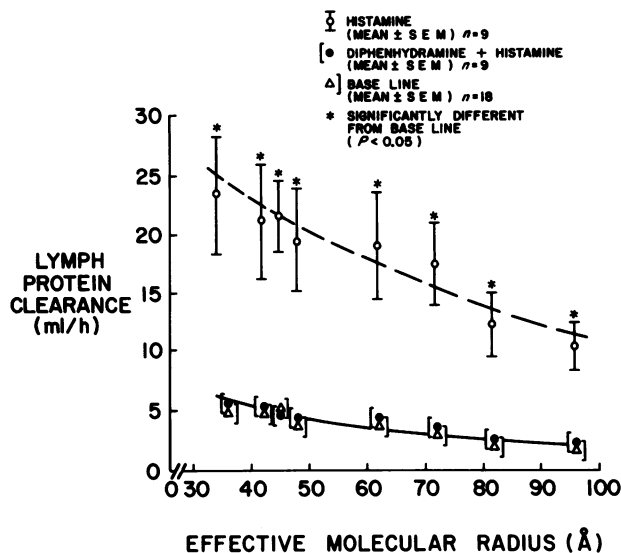


FIGURE 3 Steady-state lung lymph clearance (lymph flow \times lymph:plasma concentration ratio) for eight protein fractions as a function of estimated molecular radius during base line, histamine infusion, and diphenhydramine plus histamine infusion (see Methods for specific protocols).

pulmonary artery pressure to fall slightly less and left atrial pressure to fall more than when histamine was given alone. There was no difference between the steady-state lymph:plasma protein concentration ratios with histamine alone and with metiamide plus histamine. Lung lymph flow increased a similar amount with histamine whether or not metiamide was given.

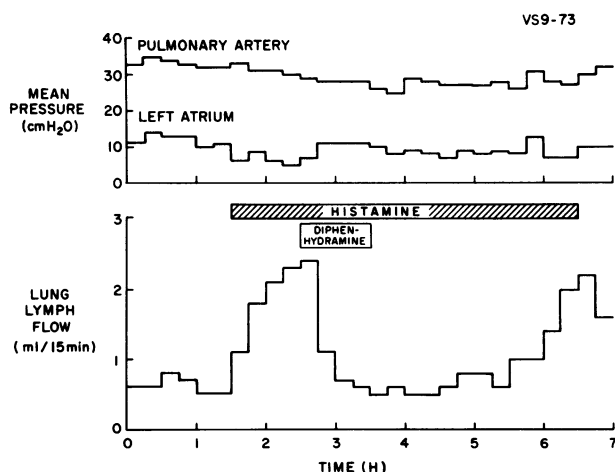


FIGURE 4 Average pulmonary arterial and left atrial pressure and lung lymph flow in an experiment where 6 mg/kg diphenhydramine hydrochloride was infused over 1 h during the response to a 4 μ g/kg per min histamine phosphate infusion.

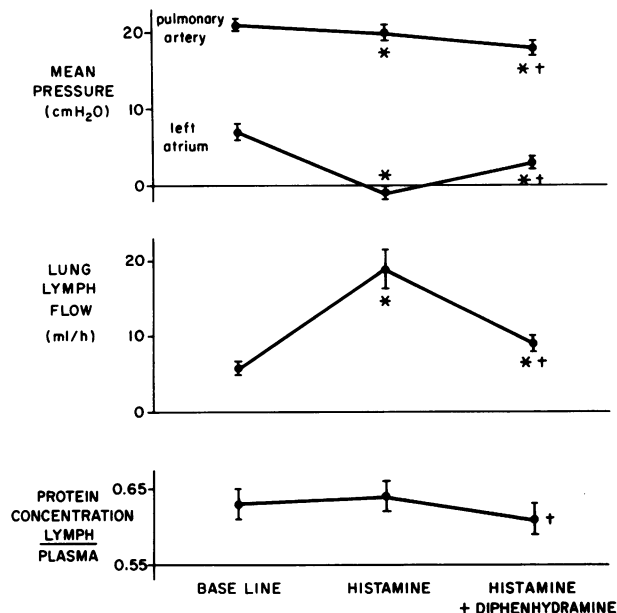


FIGURE 5 Average pulmonary arterial and left atrial pressures, lung lymph flow, and lymph:plasma total protein concentration ratios during 16 experiments like the one illustrated in Fig. 4 done in six sheep. Steady-state base-line values, values at the peak of the histamine response, and values at the maximum diphenhydramine effect are shown as mean \pm SEM.

DISCUSSION

Although some investigators have not found histamine to produce pulmonary edema in short experiments (12, 13), recent studies have clearly demonstrated that prolonged intravenous histamine infusions do cause lung water content to increase (1, 14). Pietra et al. found increased postmortem lung water in anesthetized dogs after 90-min infusions of as little as 7 μ g/kg per min histamine base (14). Histologically, the edema appeared to be primarily bronchial. We consistently found increased lung water content measured both in vivo by indicator dilution techniques and postmortem in sheep after 4-h intravenous infusions of 4 μ g/kg per min histamine phosphate (1).

Histamine has also been shown to increase microvascular permeability in the lung. Pietra et al. demonstrated leakage of carbon particles from bronchial venules caused by histamine in dogs (14). We previously reported large, sustained increases in lung lymph flow and lymph protein clearance caused by histamine infusion in unanesthetized sheep (1). Comparisons between responses to histamine and responses to mechanically increased pulmonary vascular pressures in the same animals showed that the histamine effects could not be attributed to increased pressure alone. Because intravenous histamine infusions caused a much larger lymph response than left atrial infusions, we concluded

that permeability of microvessels supplied by pulmonary artery blood was increased by histamine.

The studies reported here show that the classical antihistamine, diphenhydramine, can completely prevent both histamine-induced pulmonary edema and the increase in pulmonary vascular permeability caused by histamine. While intravenous infusions of histamine alone caused extravascular lung water, measured both by indicator dilution and postmortem methods, to increase, identical histamine infusions given during an infusion of diphenhydramine had no significant effect on lung water measured by either method. As we reported before, infusions of histamine alone caused marked, sustained increases in lung lymph flow and lymph clearance of eight protein fractions ranging from 36 to 96 Å molecular radius, indicating that pulmonary vascular permeability was increased (1, 15). Identical infusions of histamine given during an infusion of diphenhydramine had no significant effect on either lung lymph flow or lymph clearance for any of the eight protein fractions. Thus, diphenhydramine prevented the histamine effect on permeability in our preparation.

Our studies also show that diphenhydramine can reverse the histamine-induced increase in lung lymph flow and lymph protein clearance once it is established. Since diphenhydramine caused left atrial pressure to rise and pulmonary artery pressure to fall, some of the effect on lymph flow could have been secondary to redistribution of vascular resistance between pre- and postcapillary vessels (16). However, in response to changes in pressure alone, lymph:plasma protein concentration ratios relate inversely to lung lymph flow (1, 2), and diphenhydramine given during the histamine response caused both lung lymph flow and lymph:plasma protein concentration ratios to fall. The effects of diphenhydramine apparently included a decrease in the histamine-induced permeability change.

Although other investigators have found classical antihistamines capable of preventing the increase in pulmonary vascular resistance caused by histamine in isolated perfused lungs (17) and anesthetized animals (18), our studies do not demonstrate such an effect of diphenhydramine. Pulmonary vascular resistance increased a similar amount during the period of steady-state histamine response whether or not diphenhydramine was also given. The differences between our results and the results of others may be because of differences among animal species and differences among responses of unanesthetized animals, anesthetized animals, and isolated lungs. We also looked at prolonged, steady-state responses instead of short-term reactions.

Histamine has at least two kinds of effects (19). The effects which are blocked by classical antihistamines have been called H_1 receptor actions, and the effects not blocked by classical antihistamines, but blocked by other

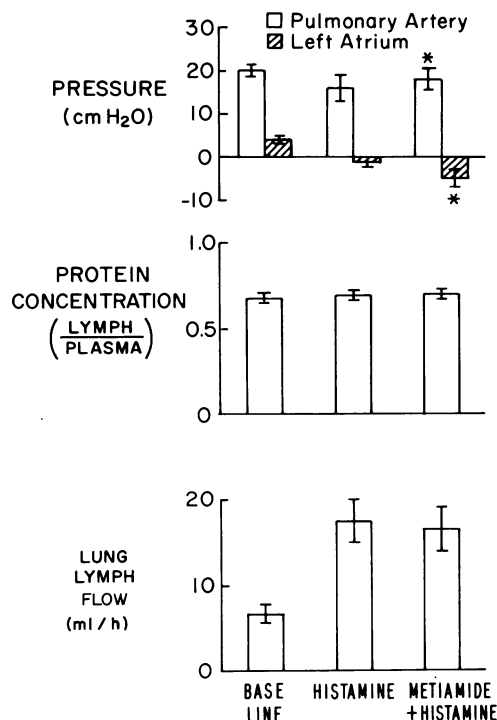


FIGURE 6 Comparison between steady-state effects of histamine alone and metiamide plus histamine on lung vascular pressures, lymph:plasma protein concentration ratios, and lung lymph flow. Values are mean \pm SEM for six pairs of studies in four sheep. Base-line values for histamine and metiamide plus histamine studies are averaged for clarity. The asterisks (*) mean that the change from base line was significantly different than with histamine alone ($P < 0.05$, paired t test). Pulmonary artery pressure fell less and left atrial pressure fell more with metiamide plus histamine than with histamine alone, but there was no difference in lymph:plasma protein ratios or lung lymph flow between the groups.

compounds (e.g., metiamide, burimamide, and beta-imide) have been called H_2 receptor actions (19, 20, 21). We found that metiamide given in doses sufficient to produce the previously reported alterations of the pulmonary hemodynamic response to histamine (19) had no effect on the histamine lung lymph response. This finding and the dramatic effects of diphenhydramine on the histamine response suggest that the increased vascular permeability caused by histamine in our preparation is an H_1 effect.

It is not known whether histamine is an important mediator in any of the clinical respiratory distress syndromes where pulmonary edema and apparent increases in lung vascular permeability occur (22). This remains a possibility, however, since histamine can have those effects and since the lung contains histamine which can be released in response to various stimuli. If histamine does cause increased lung vascular permeability and

pulmonary edema in human diseases, then classical antihistamines may be therapeutic in these disorders.

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