THE ACTION OF HISTAMINE ON THE RESPIRATORY TRACT IN NORMAL AND ASTHMATIC SUBJECTS [1]

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While investigating the systemic effects of histamine in man, Weiss and his co-workers (1, 2) observed that the intravenous injection of histamine frequently precipitated asthmatic-like attacks in patients with asthma. They also noted that it decreased the vital capacity of patients with bronchial or cardiac asthma, bronchitis or emphysema. The details of these disturbances were not reported. In view of the recent interest in antihistamine preparations, it appeared worth-while to study more thoroughly the effects of histamine on the respiratory tract in man.

METHODS

Histamine was administered to 3 groups of subjects in whom the degree of bronchoconstriction was assayed chiefly by recording the measurement of the vital capacity. The first group was comprised of 10 normal subjects. The second group included 10 patients who had a history of severe allergic disturbances, including in some a history of asthma, but who were asymptomatic at the time of observation. The third group was made up of 9 patients with varying degrees of chronic bronchitis, emphysema and asthma. An attempt was made to include in this group young, adult patients with uncomplicated continuous asthma, and to exclude patients who because of language or other difficulties could not perform the vital capacity tests without marked unaccountable variations.

Because of seasonal and other variations known to occur in asthmatic patients, one patient, B. R., a 28-year-old, single female with chronic asthma, was studied several times during the course of a 10 month period. Through training, she became an extraordinarily reliable subject, and was used for the majority of the observations. We are grateful to her for her cooperation. The other subjects were helpful mainly in confirming and enlarging the information obtained from patient B. R. Although several methods (3 to 6) have been advocated for the study of respiratory function in asthma, the determination of the vital capacity was one of the first, and is simple and fairly reliable. Since but a short period of time is required to perform the test, rapid variations in respiratory function can be detected. It was noted, however, that to do a series of vital capacity measurements in some asthmatic patients was not an easy procedure. This was due not only to fatigue, but also to coughing spells precipitated by forced expiration, especially in patients with bronchitis. A Standard Benedict Roth Metabolism Apparatus was used for the vital capacity measurements, which were recorded on a smoked drum revolving at a speed of 34 cm. a minute with a signal magnet marking 1 second intervals. By this method the slope of the expiratory curve, as well as its volume, could be studied, and bronchoconstriction distinguished from failure to perform the test with a maximal effort. While theoretically the reduction in vital capacity could be due either to bronchospasm or to edema formation, the rapidity of the changes found in this study would indicate that bronchoconstriction was the major factor. However, further studies would be needed to determine exactly the relative importance of these 2 factors in producing a decreased vital capacity after histamine.

Subjects were brought to the laboratory at least 2 hours after a meal, and were seated comfortably. No medication had been given for at least 12 hours prior to the test, and in most instances, epinephrine had been the only medication previously prescribed. During a 20-minute rest period the subject was instructed in the nature of the test, and the possible reaction that might be encountered. Assurance was given that any severe symptoms would pass away very quickly and could be promptly relieved by epinephrine. At the end of this time, from 3 to 6 vital capacities were measured to serve as controls. A varying period of time was allowed between tests in order to avoid fatigue. In subjects being studied for the first time, a greater number of tests were occasionally made until satisfactory checks were obtained. In each experiment the entire range of the control vital capacities was recorded on the charts, even though in many instances there was a good correlation between 2, 3 or 4 determinations.

The reaction of the tracheobronchial tree to histamine was then determined by injecting gradually increasing single doses of the drug into the deltoid muscle, and repeating the measurements of vital capacity. The preparation used was histamine acid phosphate, 1 ml. of which was equivalent to 0.2 mgm. of histamine base. All doses of histamine refer to the base. Much smaller amounts were then administered intravenously. Histamine was also given under the tongue and by nebulization, using the ordinary hand-type nebulizer. In these instances a more concentrated solution was employed, in which 1 ml. of histamine acid phosphate was equivalent to 1.0 mgm. of

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the base. The time of reactions and intervals between tests were measured by a stopwatch.

RESULTS AND COMMENT

In 10 normal subjects studied by this technique, no notable change in the vital capacity was observed when a dose of 0.36 mgm. of histamine was administered intramuscularly, or 0.02 to 0.03 mgm. given intravenously. Likewise, in 10 patients with a history of strong allergic tendencies, 5 of whom had a history of asthmatic attacks, no serious alteration in vital capacity was produced by similar doses of histamine. In 3 of the 5 cases with a history of asthma, a very slight reduction in vital capacity took place 30 seconds after the intravenous injection of histamine, but the change was no greater than differences observed in the control vital capacities. A study of the effect of larger doses of histamine was precluded by the severity of the side reactions.

Eight of the 9 subjects with active asthma and varying degrees of bronchitis and emphysema showed sensitivity of the tracheobronchial tree to histamine. This sensitivity varied from person to person, and in the same person varied with the degree of asthmatic symptoms (Table I). Patient P. W., a 26-year-old male with a history of wheezing and shortness of breath occurring yearly in damp weather, in whom fine wheezes could be heard throughout the lung fields at the time of the test, failed to show any notable decrease in vital capacity from a dose of 0.03 mgm. of histamine intravenously.

INTRAMUSCULAR HISTAMINE

When histamine was injected intramuscularly in sensitive asthmatic patients, a decrease in the vital capacity was observed 1 minute later, and the greatest decrease usually occurred in the second or third minutes after the injection. The vital capacity usually returned to normal within 20 to 30 minutes. Thus, in one subject, B. R., the intramuscular injection of 0.06 mgm. of histamine resulted in a drop of 1,035 ml. in the vital capacity, from the control level of 3,155 ml. to 2,120 ml. in 1 minute. At 2 minutes the vital capacity had decreased further to 1,920 ml., and 3 minutes after the injection it measured 1,955 ml. At 30 minutes the vital capacity had returned to near the control range, and measured 3,050 ml. When gradually increasing dosages, ranging from 0.02 to 0.16 mgm., of histamine were injected at intervals intramuscularly, increasing amounts of bronchoconstriction were produced (Figure 1). When gradually decreasing dosages were employed, ranging from 0.16 mgm. down to 0.02 mgm., decreasing amounts of bronchoconstriction were produced (Figure 2). The decrease in vital capacity produced by identical amounts of histamine injected intramuscularly, regardless of the order of dosage, was similar, and appeared to rule out any notable cumulative effect of the drug (Table II). Four consecutive doses of 0.06 mgm. of histamine injected intramuscularly at 30-minute intervals produced similar amounts of reduction in the vital capacity (Figure 3). Slightly accelerated histamine effects occurred after several intramuscular injections in the same region, and it was felt that continued local vasodilation due to repeated histamine injections resulted in more rapid absorption. The flush and headache following the histamine injections appeared no more severe in asthmatic subjects than in normals.

TABLE I

The effect on the vital capacity of histamine given parenterally to asthmatic subjects

Patient	Age	Sex	Histamine intramuscularly			Histamine intravenously		
			Dosage	Reduction in vital capacity		Dosage	Reduction in vital capacity	
			mgm.	*ml.*	*per cent*	*mgm.*	*ml.*	*per cent*
J. D.	16	F	0.08	420	15	0.02	1,944	63
B. Y.	72	M	0.12	720	30	0.02	836	34
V. B.	49	M	0.16	408	9	0.02	2,874	68
C. C.	48	M	0.16	700	23	0.03	1,160	35
A. L.	33	M	0.20	732	14	0.03	1,338	27
M. K.	54	F	0.08	313	16	0.03	659	32
J. H.	38	M	0.08	628	11	0.02	1,498	28
B. R.	29	F	0.08	982	33	0.02	2,048	71
P. W.	26	M	0.02	no change		0.03	no change	

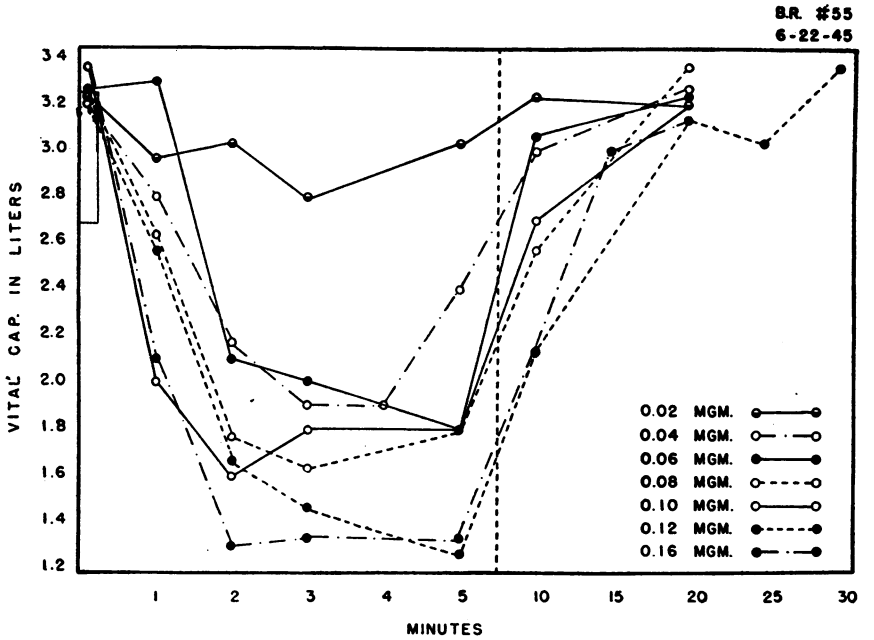

FIG. 1. EFFECT OF I.M. HISTAMINE. GRADUALLY INCREASED DOSAGE

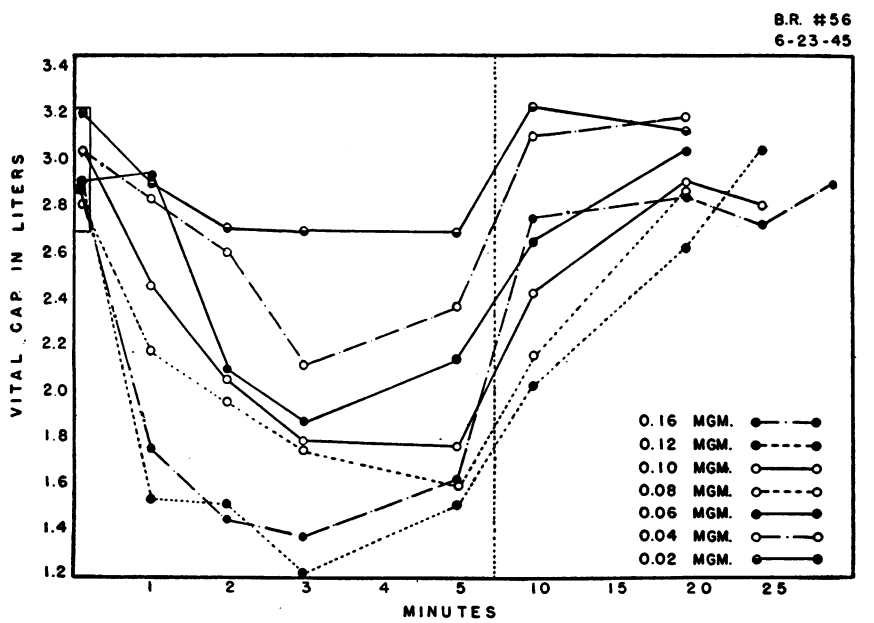

FIG. 2. EFFECT OF I.M. HISTAMINE. GRADUALLY DECREASED DOSAGE

TABLE II

Comparison of the effect on the vital capacity of progressively increasing and progressively decreasing the amounts of histamine injected intramuscularly in an asthmatic subject

Histamine intramuscularly	Vital capacity	
	Increasing dosage	Decreasing dosage
mgm.	*ml.*	*ml.*
control	3,240	3,200
0.02	(1) 2,800	(7) 2,700
0.04	(2) 1,922	(6) 2,135
0.06	(3) 1,812	(5) 1,890
0.08	(4) 1,650	(4) 1,620
0.10	(5) 1,600	(3) 1,780
0.12	(6) 1,297	(2) 1,225
0.16	(7) 1,318	(1) 1,380

Numbers in parentheses refer to the order of injection.

INTRAVENOUS HISTAMINE

After sensitivity of the tracheobronchial tree to histamine by the intramuscular injection had been determined in the reactive subjects, the drug was then given intravenously. Depending on the weight of the patient, the degree of tracheobronchial sensitivity, and the degree of side reactions, doses of from 0.01 to 0.04 mgm. of histamine were injected. Patients weighing less than 50 kgm. were ordinarily given not more than 0.02 mgm. of histamine intravenously in a single injection. As might be expected when histamine was given by this route, bronchoconstriction was more marked, and appeared more quickly. A definite decrease in vital capacity could be demonstrated within 9 seconds after the intravenous injection of 0.03 mgm. of histamine. Since the arm-to-tongue circulation time varied from 12 to 20 seconds with histamine given intravenously, it was felt that this rapid reaction represented an effect from diffusion through the pulmonary artery and vein. The most marked effect was found to occur 30 seconds after the completion of the injection. It wore off very rapidly, so that in 5 to 10 minutes the vital capacity had returned nearly to the control levels. For example, in one test the injection of 0.02 mgm. of histamine intravenously resulted in a drop in vital capacity of 1,960 ml., from the control level of 3,240 ml. to 1,280 ml. in 30 seconds. By 1½ minutes after the injection the vital capacity had increased to 1,780 ml., and at 2½ minutes had risen to 1,905 ml. A gradual return to the control level then occurred in 20 minutes.

With successive intravenous injections of similar amounts of histamine at 30-minute intervals, similar amounts of bronchoconstriction took place, but there appeared a tendency for the effect to wear off a little more quickly with each injection.

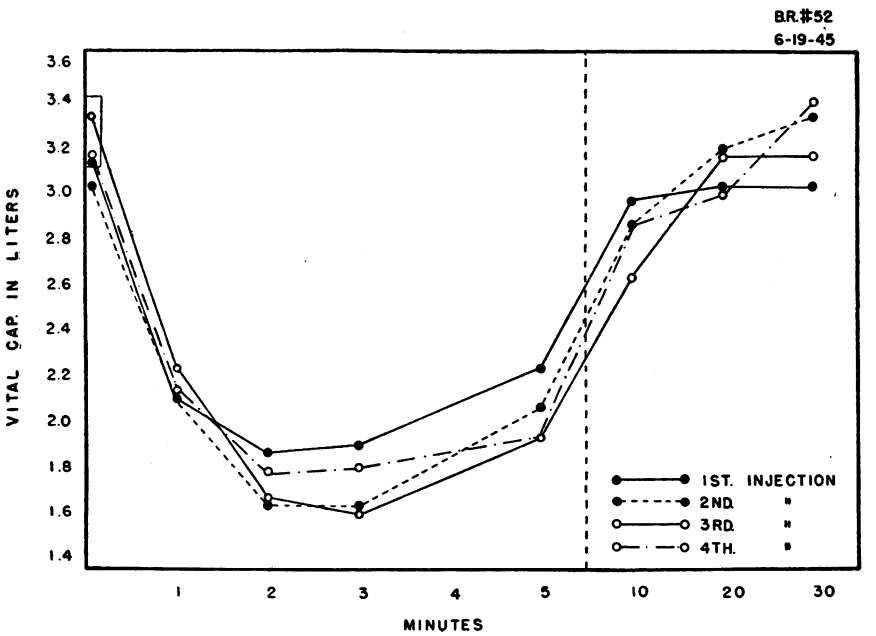

FIG. 3. EFFECT OF 0.06 MGM. I.M. HISTAMINE EVERY 30 MINUTES

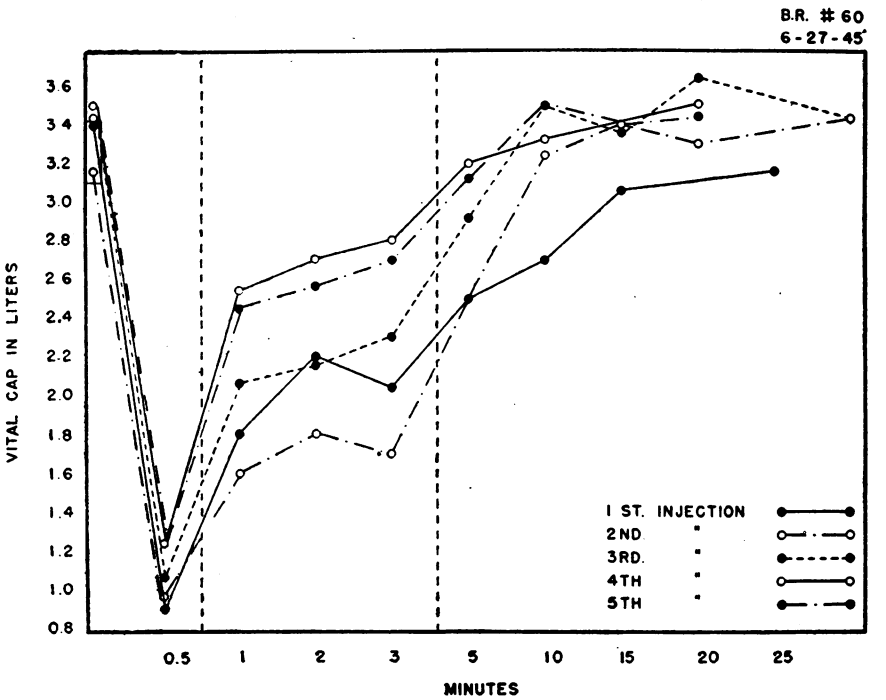

FIG. 4. EFFECT OF 0.04 MGM. I.V. HISTAMINE EVERY 30 MINUTES

For example, in subject B. R., 5 successive intravenous injections of 0.04 mgm. of histamine, at 30-minute intervals, resulted in decreases of 2,470 ml., 2,205 ml., 2,355 ml., 2,175 ml. and 2,225 ml., respectively, in the vital capacity (Figure 4). In order to determine whether additive amounts of histamine would have effect while the tracheobronchial tree was still reacting to a preceding injection of histamine the following tests were performed. In one instance, after the injection of 0.01 mgm. of histamine had reduced the vital capacity to 1,855 ml. in 30 seconds, the injection was repeated 30 seconds later, and a further reduction in the vital capacity to 1,615 ml. resulted. In another instance the second injection was given 1½ minutes later, and again a further decrease in vital capacity occurred. However, when the total dosage of 0.02 mgm. was given in a single injection, a greater reduction in vital capacity was achieved with a fall to 1,280 ml. (Figure 5). These studies indicate, then, that during any period of observation, similar amounts of bronchoconstriction can be produced when identical amounts of histamine are injected either intravenously or intramuscularly. It was a matter of great interest to determine whether this sensitivity was variable, and it was soon noted that the degree of sensitivity varied with the severity of asthmatic symptoms. Occasionally an increase in sensitivity would manifest itself by a delay in the appearance of the greatest amount of bronchoconstriction. For example, after the intravenous injection of histamine, the greatest decrease in vital capacity would be noted at 1½ minutes, rather than at 30 seconds, and the return towards the normal range would also be delayed. Incidentally, it was also observed that the relief afforded by sympathomimetic amines against histamine bronchoconstriction was less at these times. In one instance, the intravenous injection of 0.02 mgm. of histamine reduced the vital capacity from 2,884 ml. to 836 ml., a drop of 2,048 ml., and 1½ hours were required before it returned to near the control range.

An irregular but definite bronchoconstriction occurred when 0.35 mgm. of histamine was placed under the tongue. The decreased vital capacity returned to normal after the mouth had been rinsed with saline. The nebulization of 1 : 1,000 histamine into the lung also produced a reduction in vital capacity. Four inhalations of 1 : 1,000 solution of histamine by nebulizer produced a notable reduction in vital capacity (Figure 6).

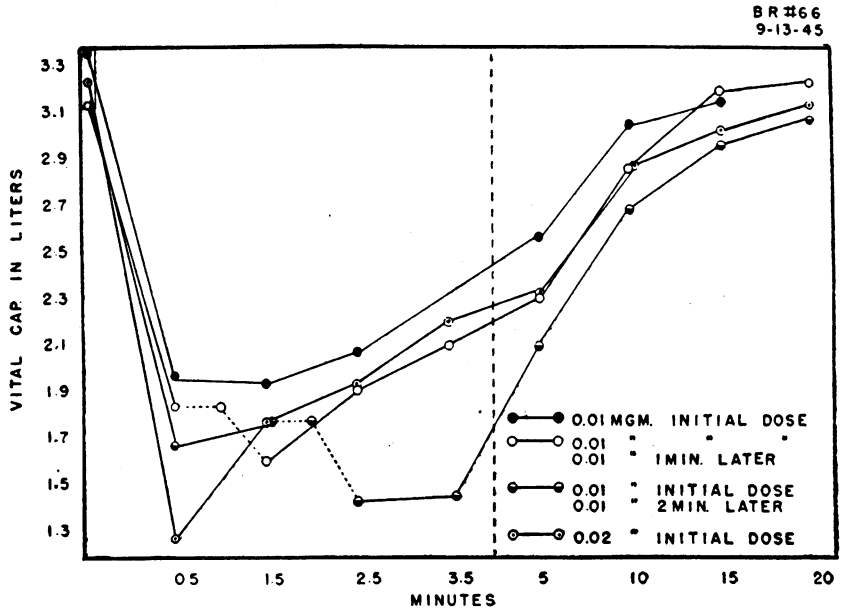

FIG. 5. EFFECT OF REPEATED DOSES I.V. HISTAMINE

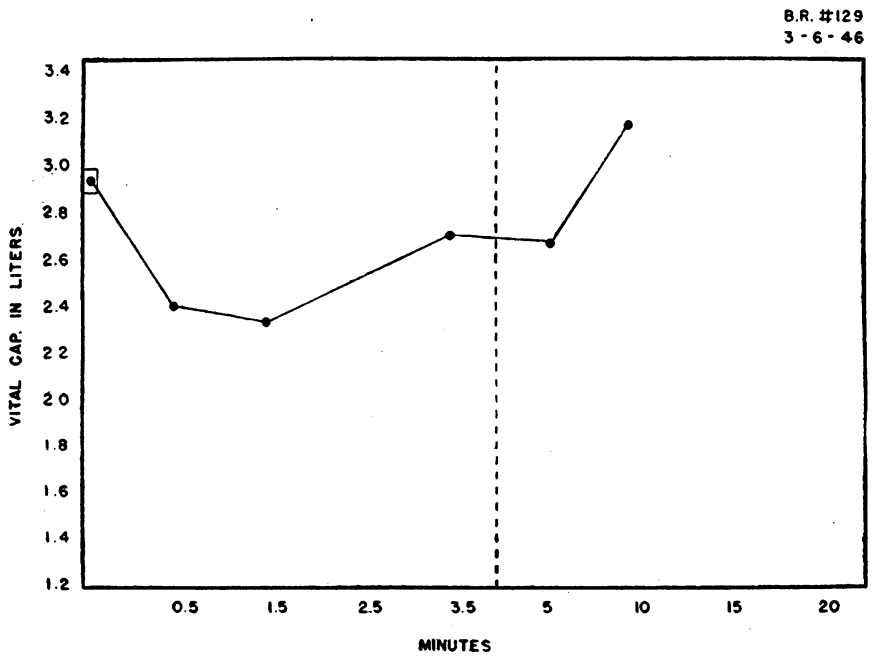

FIG. 6. EFFECT OF NEBULIZATION OF 1:1,000 HISTAMINE

The type of reaction resembled that produced by the intravenous administration of the drug.

SUMMARY

1. The reaction of the tracheobronchial tree to histamine was investigated in 10 normal subjects, 10 patients with a history of severe allergic tendencies, and 9 patients with varying degrees of bronchitis, emphysema and asthma. In the first 2 groups, no notable reduction in vital capacity was observed after the intramuscular injection of a dose of 0.36 mgm., or the intravenous administration of a dose of 0.02 to 0.03 mgm. of histamine. In the third group, the sensitivity of the tracheobronchial tree to histamine in asthmatic subjects was confirmed in 8 of the 9 patients. This sensitivity was found to vary from patient to patient, and with the degree of asthma.

2. During any one period of observation, quantitatively similar amounts of bronchoconstriction, as measured by a decrease in the vital capacity, could be produced by identical amounts of histamine injected at intervals by either the intramuscular or intravenous route. Bronchoconstriction may also be induced by administering histamine under the tongue, or by nebulization.

3. No evidence was adduced to show that the systemic reactions to histamine in asthmatic subjects differed from the systemic reactions in normals.

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