

From: Asthma & Allergy Research Unit, St. David's Hospital, Cardiff.
Wales, Gt. Britain.

PROVOCATION OF BRONCHIAL OBSTRUCTION IN BRONCHIAL ASTHMA BY DILUTE HISTAMINE AEROSOLS

By

H. HERXHEIMER

It is well known that histamine can be used to provoke attacks in asthmatics. *Weiss et al.* (6) and *Samter* (5) have given it intravenously, *Curry* (1), *Curry & Lowell* (2) and others as an aerosol. I have shown that a 3 per cent histamine diphosphate aerosol, breathed from a closed spirometer circuit, caused an asthmatic attack in the 30 patients investigated within 8 to 150 sec. In 4 of 12 normal subjects, however, 3 min inhalation caused only a slight feeling of tightness in the chest and no asthma (3). This distinction between normals and asthmatics has since been used to confirm the diagnosis of asthma or related disorders in the few cases where it was in doubt.

An attack of asthma can also be provoked by allergen aerosols, and this method has been used for diagnostic purposes increasingly during the last 25 years. When I compared the effect of dilute and of concentrated antigenic aerosols, the surprising result was that the same amount of antigenic matter had a stronger effect if it was given in a diluted form over a long period of time (4). A plausible explanation of this phenomenon has, so far, not been found, but the question must be asked, whether, perhaps, the greater dispersion of the asthma provoking particles could be the reason for

their stronger action. If this were the case, the same difference should be found between a concentrated and a dilute histamine solution given as an aerosol by the same method. This paper describes experiments to elucidate this point.

METHOD

The methods of aerosol exposure and measuring lung function were used as described in earlier experiments (6). Nine patients with mild or moderate asthma, mostly of allergic origin, were investigated. The purpose of the trial was explained to them and they agreed to take part. In each patient the suitable histamine concentration and the necessary exposure time had to be found before the start of the experiment. In all patients the 0.1 per cent solution was tried at first. The patient was exposed to the aerosol of Coca's solution as a placebo test beforehand and was asked to give a sign as soon as he felt tightness in his chest. If this did not happen, he was changed to 0.1 per cent histamine. This was stopped if the patient gave his sign, but at the latest after 100 sec. If, at that time, no bronchial spasm had occurred, the experiment was broken off and a higher concentration used at the next time: 0.5 per cent in 2 patients and 2 per cent in one patient.

When, according to the subjective feeling of the patient, tightness of the chest (or cough) occurred, inhalation was stopped at once, the spirometer circuit washed out, and peak flow and vital capacity (non-forced) determined. This had also been done before the start of the inhalation. These lung function tests were then repeated at 2-5 min intervals until they had returned to their basal values. This usually was the case after 20-30 min.

Not in all cases was it possible to hit on the threshold histamine dosage in the first experiment. In 4 experiments the bronchial obstruction caused was so strong that isoprenaline had to be given to abort the attack. This, naturally,

Remarks:

- ¹⁾ In either experiment no change of lung function, but a definite wheeze.
- ²⁾ In either experiment cough and sore feeling in chest.
- ³⁾ Attack after dilute histamine milder, possibly because of underexposure.
- ⁴⁾ Underexposure with dilute histamine (120 instead of 180 sec) caused a milder attack.
- ⁵⁾ Underexposure (250 sec instead of 396 sec) caused an attack of about the same intensity.
- ⁶⁾ In spite of underexposure (198 sec instead of 240 sec) the attack was stronger.
- ⁷⁾ Exposure to dilute histamine after interval of 42 min.
- ⁸⁾ Exposure to dilute histamine after interval of 150 min.

TABLE 1
At each date there were 2 consecutive experiments, first with the basic histamine
concentration and second with a dilution of it.

Patient	Date	Hist. concentra- tion %	Degree of hist. diffu- sion	Expos. period sec.	Degree of extension of expos. period	Before exposure v.c.	p.f.	Max. decrease of p.f. after histamine in per cent	Remarks
F.	18.12.	0.1	—	80	—	3040	440	5	3 ¹⁾
		0.033	3 fold	240	3 fold			2	5
	11.5.	0.25	—	43	—	2980	450	40	20 ²⁾
		0.033	7½ fold	322	7½ fold			7	12
Ha.	22.5.	0.1	—	100	—	4640	270	18	44
		0.033	3 fold	250	2½ fold			14	40 ³⁾
	16.5.	0.5	—	8	—	4740	245	8	29
		0.0167	30 fold	240	30 fold			2	29
	11.5.	0.25	—	20	—	5040	340	1	18 slight wheeze
		0.033	7½ fold	130	7½ fold			2	22 no wheeze
Hi.	8.1.	0.1	—	65	—	3640	345	20	53 mild wheeze
		0.0167	6 fold	390	6 fold			28	47 mild wheeze
	2.7.	2.0	—	100	—	3990	440	8	23 mild wheeze
		0.5	4 fold	400	4 fold			18	30 mild wheeze
M.	20.2.	0.1	—	100	—	3645	260	13	37 mod. wheeze ³⁾
		0.0167	6 fold	480	5 fold			6	27 less wheeze
	22.5.	0.1	—	150	—	3590	275	2	18 little wheeze
		0.0167	6 fold	860	6 fold			4.2	12 no wheeze
	7.7.	0.1	—	130	—	3400	265	37	55
	27.11.	0.0167	6 fold	750	6 fold			13	61 simil. react.
		0.5	—	32	—	3570	285	11	30

	0.033	15 fold	480	15 fold	230	2280	230	7	22	simil. react.
Mc.	0.1	—	35	—	—	—	—	—	—	—
	0.0167	6 fold	210	6 fold	—	—	—	8	30	simil. react.
16.3.	0.1	—	25	—	—	—	—	3	14	—
	0.0167	6 fold	150	6 fold	—	—	—	4	18	simil. react.
R.	0.1	—	50	—	—	—	—	19	22	—
	0.0167	5 fold	300	5 fold	—	—	—	4	22	simil. react.
P.	0.1	—	15	—	—	—	—	13	12	—
	0.0167	6 fold	90	6 fold	—	—	—	13	20	simil. react.
16.2.	0.1	—	20	—	—	—	—	15	10	—
	0.0167	6 fold	120	6 fold	—	—	—	11	21	simil. react.
16.3.	0.1	—	20	—	—	—	—	19	24	—
	0.0055	18 fold	360	18 fold	—	—	—	21	12	simil. react.
A.	0.1	—	60	—	—	—	—	18	55	¹⁾
	0.033	3 fold	130	2.2 fold	—	—	—	3	22	—
25.8.	0.1	—	22	—	—	—	—	10	15	—
	0.0055	18 fold	250	11 fold	—	—	—	15	13	⁶⁾
8.1	0.1	—	40	—	—	—	—	8	17	—
	0.0167	6 fold	198	5 fold	—	—	—	25	40	⁶⁾
B.	0.5	—	35	—	—	—	—	33	15	—
	0.033	15 fold	375	11 fold	—	—	—	35	22	—
7.2.	0.5	—	35	—	—	—	—	36	21	—
	0.033	15 fold	180	5 fold	—	—	—	15	17	—
14.2.	0.5	—	30	—	—	—	—	48	43	—
	0.033	15 fold	70	2.3 fold	—	—	—	6	17	⁵⁾
14.3.	0.5	—	26	—	—	—	—	50	43	—
	0.033	15 fold	55	2 fold	—	—	—	13	24	⁶⁾

v.c. = non-forced vital capacity. p.f. = maximum expiratory flow.

Remarks see p. 213.

precluded a further experiment on the same day. When, however, a mild attack was provoked, as intended, the patient was given as much time as he needed for recovery of lung function. When this was complete, a second exposure with histamine dilution followed, either 0.033 per cent (a sixfold dilution of the 0.1 per cent solution), or 0.0167 per cent, a twelvefold, or 0.0055 per cent, a thirty-six-fold dilution. The duration of exposure was prolonged accordingly: if, for instance, the 0.1 per cent solution had caused mild bronchial obstruction after 45 sec, a 0.0167 per cent solution was given for 6 times 45 = 270 sec and the change of lung function after this exposure recorded as before.

Wherever possible, dilutions of different degrees were used in the same subject in different experiments, and 2 or 3 experiments were done with each patient. In one subject (R.) only one dilution experiment could be done, as the patient was not available later on.

RESULTS

These are given in Table 1. It can be seen that 7 of the 9 subjects reacted in the same way. If the aerolized histamine solution was diluted 5 to 30 fold and the exposure time prolonged in the same proportion, the resulting bronchial obstruction was about the same, subjectively and in the degree of decreased lung function. In 2 experiments (Ha. and M.) the dilution exposure was a few seconds shorter than it should have been, but the lung function tests and the subjective response showed in these experiments lesser changes than in the preceding test with the undiluted histamine. It is therefore unlikely that a slightly longer exposure with an undiluted histamine would have caused a stronger attack than the undiluted solution.

The remaining subjects A and B reacted differently. It was not possible to expose A to the dilute histamine aerosol for the complete appropriate period. In each of 3 experiments a wheeze appeared much earlier, and the exposure had to be broken off; a fourth experiment had a borderline result. In patient B the same happened in 4 experiments, although, after the exposure with undiluted histamine, the lung function had completely recovered, as it had in patient A. It was suspected that in both patients some remaining histamine effect persisted in spite of the normal lung function and of the abs-

ence of any complaint 30 min after exposure to the undiluted histamine. For this reason, an interval of 2½ hrs was put between the first and the second exposure in the last experiment with B, but the result was the same as before. This patient then offered the information that, on 2 different occasions, he had experienced mild and transient wheezes on the afternoon or evening after the experiment, and once also on the following morning.

DISCUSSION

In 7 out of 9 patients, the same amount of histamine aerosol, whether dilute or not, gave always about the same reaction in the same patient, if the experiments were done on the same day. In the 2 other patients, some bronchial irritability seems to have remained after the histamine inhalation, so that the present method could not be applied to them. Their reaction might also have been a psychological one, although this is improbable in view of their prior negative reaction to Coca's solution, a placebo test. Unfortunately, we have not been able to give another placebo inhalation to these 2 patients before the dilute aerosol exposure.

The present results contrast sharply with the previously described effect of dilute antigenic aerosols, when the dilute administration had a stronger action. This lends some weight to the hypothesis that with antigens, the duration of its intimate contact with the mucous membrane is more important than its concentration. With histamine, a comparatively simple molecule, its reaction with the membrane may take considerably less time. The present results show that the greater dispersion of the histamine particles in the diluted solution does not enhance its effect.

SUMMARY

1. In 9 asthmatic subjects the degree of bronchial obstruction after aerosol inhalation of the same amounts of histamine

in concentrations between 0.1 and 5 per cent, and, subsequently, in 3 to 30 fold dilutions of the previously used concentration, was measured.

2. In 7 of these subjects the degree of bronchial obstruction caused was about the same, regardless of dilution and duration of exposure, as long as the amount of histamine inhaled remained the same. In 2 other patients, histamine seemed to have a long lasting effect so that the present method could not be applied to them.

3. It is concluded that the same amount of histamine has the same effect on the bronchial membrane, whether dilute or not. This is in contrast to antigen aerosol whose effect in dilution is stronger.

ACKNOWLEDGMENTS

I am grateful to Dr. D. A. Williams, F.R.C.P., Asthma and Allergy Research Unit, St. David's Hospital, Cardiff for access to his patients and for his continuous support; and to the Welsh Hospital Board for a grant for travel expenses.

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