

Assessment of bronchodilatation after spontaneous recovery from a histamine challenge in asthmatic children

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Abstract

Background It would be convenient to be able to measure airway responsiveness to histamine and to bronchodilator drugs on the same day, but whether this can be done reliably is unknown.

Methods The effect of a prior histamine challenge on the bronchodilator response to salbutamol after spontaneous recovery of FEV₁ to 95% of the pre-challenge level was studied in two groups of asthmatic children. Fourteen children inhaled 400 µg salbutamol after spontaneous recovery from a histamine challenge, followed by a further 100 µg salbutamol 20 minutes later. In a second group of eight asthmatic children the study was repeated with 800 µg salbutamol, followed by a further 200 µg 20 minutes later.

Results After histamine challenge FEV₁ returned to baseline in 70 minutes or less on all occasions. The FEV₁ 20 minutes after 400 µg salbutamol was significantly lower after the histamine challenge than on the control day. After the further 100 µg salbutamol FEV₁ values were similar after the histamine challenge and on the control day. FEV₁ values after 800 µg salbutamol and the further 200 µg dose were not influenced by a prior histamine challenge.

Conclusions In children with stable asthma in whom FEV₁ has returned to baseline after a histamine challenge the FEV₁ achieved after 800 µg salbutamol is not affected by the histamine challenge. Histamine and bronchodilator responsiveness can thus be assessed reliably on the same day in patients with stable asthma. This has clear advantages for patient care.

Airway responsiveness to β_2 sympathomimetic drugs and to histamine or methacholine are often considered as indicators of asthma severity when asthma is stable. Both tests have an important role in the clinical assessment of asthma and in research¹; it would be convenient if they could be carried out on the same day.

Combining a bronchodilator and a bronchoconstrictor test on the same day might, however, produce unreliable findings. There is ample evidence that β_2 agonists protect against histamine induced bronchoconstriction for

several hours.² The effect of a histamine challenge on histamine responsiveness has also been investigated,^{3,4} but little is known about the effect of acute histamine induced bronchoconstriction on a subsequent bronchodilator test.

A histamine challenge may affect the response to a β_2 agonist even after airway calibre has returned to baseline. Histamine is metabolised within minutes⁵ and does not accumulate, provided that several minutes are allowed between inhalations⁶; histamine, however, may reduce air flow for longer.⁷ The forced expiratory volume in one second (FEV₁) recovers within 60 minutes of histamine administration,⁸ the recovery time being positively correlated with the dose of inhaled histamine and the magnitude of the response.^{8,9} Thus some of the bronchoconstriction is not short lived. The mechanisms of recovery from a histamine challenge are poorly understood.

The purpose of this study was to investigate the effect of a prior histamine challenge on bronchodilatation with salbutamol after spontaneous recovery of FEV₁ to the baseline level, to assess whether the two tests can be performed reliably on the same day.

Methods

PATIENTS

Subjects were selected from the outpatient clinics for respiratory medicine of the Juliana and Sophia Children's Hospitals in The Hague and Rotterdam. Criteria for inclusion were: (1) asthma that was stable for three weeks before the study; (2) baseline values of FEV₁ of 50–90% of predicted or an FEV₁/FVC of 60–75%, or both; (3) dose of histamine that reduced FEV₁ by 20% (PD₂₀) less than 150 µg; (4) ability to perform forced expiratory manoeuvres reproducibly; (5) age 7–14 years. All medication was discontinued before the tests (eight hours in advance for inhaled drugs and 48 hours for oral drugs). The study was carried out with the informed consent of both children and parents, and was approved by the local medical ethics committee.

BRONCHODILATOR RESPONSE AND BRONCHIAL HYPERRESPONSIVENESS

FEV₁ was measured with a rolling seal spirometer (Vicat 5, 10 litre volume displacement) with a resolution of 20 ml, connected to a computer. The spirometer was heated

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to 35.5°C; volumes were corrected to BTPS. The best of three technically satisfactory FEV₁ measurements was recorded¹⁰ and expressed as percentage of the predicted value.¹¹

Bronchodilation was assessed from two sequential inhalations of salbutamol at 20 minute intervals. A two step administration of salbutamol was preferred to a single administration because it might result in a greater increase in FEV₁, as a result of better penetration of the second dose when some bronchodilation has been achieved.¹² Salbutamol was administered from a metered dose inhaler with a spacer (Volumatic), the dose depending on the protocol: puffs contained 100 µg (protocol 1) or 200 µg salbutamol (protocol 2). Salbutamol was inhaled during a single slow inspiration from functional residual capacity to total lung capacity immediately after each actuation. The breath was then held for about 10 seconds before exhalation. This was done on four occasions and FEV₁ was recorded 20 minutes after each dose of salbutamol. One more puff was then inhaled in the same fashion and FEV₁ was again measured 20 minutes later.

Aerosolised histamine diphosphate was inhaled from a calibrated DeVilbiss 646 nebuliser with its vent closed and primed with 3 ml solution. The nebuliser was attached to a Rosenthal-French dosimeter driven by air at 137.8 kPa (20 lb/in²). The aerosol was delivered directly into the mouth through a mouth tube. The subject inspired as slowly as possible from functional residual capacity to total lung capacity. During the inspiration the dosimeter was triggered for 0.6 seconds. At the end of the inspiration the children were asked to hold their breath for about two seconds. With this technique lung deposition should be maximal.¹³ A total of 20 µl of histamine solution was delivered to the mouth in four consecutive breaths. Histamine diphosphate in buffered saline was given in doubling concentrations (0.25–32 mg/ml). PD₂₀ was calculated by interpolation of the dose-response curve on a log-linear scale.¹⁴

STUDY PROTOCOLS

Protocol 1

Children were investigated in a randomised crossover design at about the same time of the day on two days within two weeks. On the control day a baseline measurement of FEV₁ was followed by four inhalations of 100 µg salbutamol and a further measurement of FEV₁ 20 minutes later. A further 100 µg salbutamol was then administered and FEV₁ measured again after 20 minutes. On the histamine challenge day baseline measurement of FEV₁ (baseline 1) was followed by a histamine challenge test until FEV₁ fell by 20%. FEV₁ was then allowed to recover spontaneously. Recovery was monitored 60 and 70 minutes after the end of the histamine challenge. It was regarded as complete when FEV₁ had returned to at least 95% of baseline 1 in 70 minutes (baseline 2). Seventy minutes after the histamine challenge the two step broncho-

dilation was measured as on the control day. Subjects were excluded when complete recovery was not achieved, or when the baseline FEV₁ measurement on the first day differed more than 10% from that on the second day.

Protocol 2

The design was the same as in protocol 1, except that twice as much salbutamol was administered, puffs of 200 µg each being used. Four inhalations of 200 µg salbutamol were administered, followed by one inhalation of 200 µg salbutamol 20 minutes later.

DATA ANALYSIS

The hypothesis tested was that change in FEV₁ after a given dose of salbutamol would be the same with as without a prior histamine challenge. Post-bronchodilator FEV₁% predicted and increase in FEV₁% predicted were analysed by means of two tailed paired *t* tests, with the level of significance set at *p* = 0.05. Differences were reported as means with 95% confidence limits (CL). A significant difference in post-bronchodilator FEV₁ was defined as a difference greater than the standard deviation of the reproducibility of FEV₁% predicted before bronchodilation in asthmatic children. In 78 children with stable asthma this was 3.52% predicted, and independent of the level of FEV₁% predicted, age, and sex (own observations). From this it can be calculated that 12 subjects would be required to detect a difference in post-bronchodilator FEV₁ of 4% predicted (the 75th percentile of this reproducibility) with a power of 80%.

Results

PROTOCOL 1

Of the 19 children who took part in the study, five failed to complete it, three for personal reasons and two because FEV₁ recordings on the second day differed by more than 10% from those on the first day. Nine boys and five girls (age range 8.1–13.5 years) completed protocol 1 (table 1). FEV₁ had returned to baseline values in 11 children within 60 minutes, and in all after 70 minutes. There were no significant differences between baseline 1 and 2 FEV₁ values before and after histamine (mean difference –0.2% predicted, 95% CL –2.5, 2.2), or between baseline on the control day and baseline 1 on the histamine challenge day (mean difference 0.5% predicted, 95% CL –1.1, 2.2) or baseline 2 on the histamine challenge day (mean difference 0.4% predicted, 95% CL –2.0, 2.8).

Twenty minutes after administration of 400 µg salbutamol FEV₁ was significantly smaller on the histamine challenge day than on the control day (mean difference –4.2% predicted, 95% CL –7.4, –0.9; *p* = 0.016). After a further 100 µg salbutamol FEV₁ did not differ from that on the control day (mean difference –0.7% predicted, 95% CL –3.4, 2.0; fig 1). Change in FEV₁% predicted after 400 µg salbutamol on the control day was

Table 1 Effects of previous histamine challenge on bronchodilator response assessed by FEV₁: protocol 1

Patient No	Age (y)	Height (cm)	Sex	Order*	PD ₂₀ (µg)	FEV ₁ (% predicted)					
						Histamine challenge day			Control day		
						Baseline†	Salbutamol		Baseline	Salbutamol	
							1	2		After 400 µg	After a further 100 µg
1	8.5	130	F	1	49	72.2	76.9	81.6	91.1	74.3	92.8
2	10.5	145	M	2	60	74.2	74.9	78.7	80.6	77.5	83.9
3	8.1	133	M	1	20	86.9	84.3	95.1	95.7	80.7	93.8
4	12.9	151	M	1	19	85.9	81.9	92.5	94.9	85.2	96.1
5	9.4	144	F	1	44	75.7	76.8	81.8	92.6	81.3	89.6
6	10.3	161	M	2	36	72.3	69.4	77.3	76.4	73.2	81.8
7	13.4	148	M	2	38	93.7	90.4	95.2	95.5	91.0	94.9
8	8.4	128	M	2	23	89.0	98.3	99.2	109.4	90.5	103.3
9	11.8	138	M	2	58	82.9	86.3	93.0	92.9	83.4	96.0
10	8.4	128	F	2	5	73.0	68.8	88.2	91.0	73.5	88.9
11	10.8	144	M	1	40	71.4	72.7	82.5	77.7	71.8	78.5
12	10.6	138	F	2	27	84.9	84.2	93.5	90.1	84.4	98.2
13	13.5	167	F	1	22	70.9	74.1	74.8	97.4	70.3	93.2
14	13.3	152	M	1	23	76.7	72.9	91.9	96.1	80.2	92.7
Mean	10.7	143			32†	79.3	79.4	87.5**	91.5	79.8	91.7
SD	1.9	11				7.7	8.5	7.8	8.6	6.7	6.7

*1—Starting with histamine challenge test; 2—starting with control experiments.
†Geometric mean. ‡Baseline 1—before histamine challenge; baseline 2—70 minutes after histamine challenge.
**Significantly different from the control day after inhalation of 400 µg salbutamol (p < 0.02, Student's *t* test).

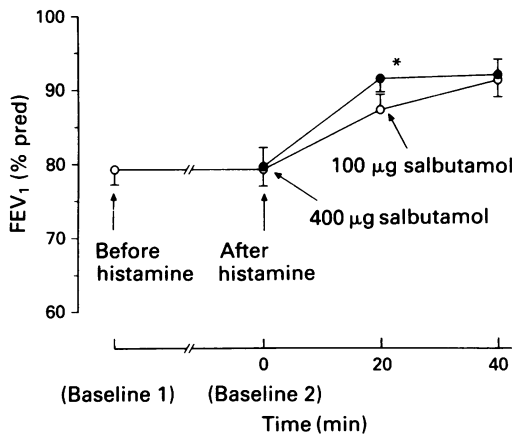


Figure 1 Mean (SE) FEV₁ (% predicted) from protocol 1 (n = 14). Data refer to the control day (closed symbols) and the histamine challenge day (open symbols). *p = 0.02.

significantly greater than on the histamine challenge when this was related to baseline 1 or pre-histamine FEV₁ (mean difference 3.6% predicted, 95% CL 0.4, 6.8) but not when this was related to baseline 2 or post-histamine FEV₁ (mean difference 3.1% predicted, 95% CL -0.7, 8.2). The difference is because in one subject (No 8), whose FEV₁ after recovery from histamine was 10% predicted higher than that before histamine. Change in FEV₁ after the final 100 µg salbutamol was similar on the two days (mean difference -0.4% predicted, 95% CL -3.8, 3.0).

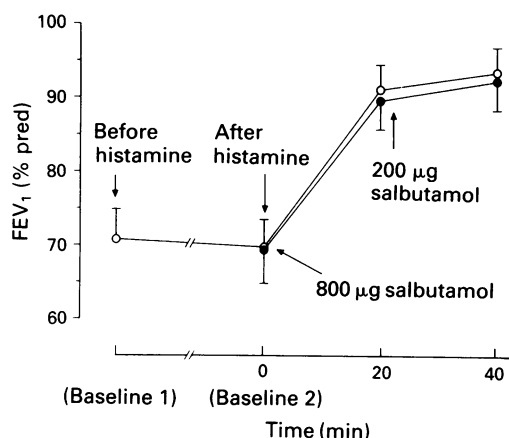
PROTOCOL 2
Of the 10 participants, two boys were excluded because baseline 1 values for FEV₁ on the second day differed by more than 10% from those on the first day; six boys and two girls completed protocol 2 (table 2). There were no

Table 2 Effects of previous histamine challenge on bronchodilator response assessed by FEV₁: protocol 2

Patient No	Age (y)	Height (cm)	Sex	Order*	PD ₂₀ (µg)	FEV ₁ (% predicted)					
						Histamine challenge day			Control day		
						Baseline†	Salbutamol		Baseline	Salbutamol	
							1	2		After 800 µg	After a further 200 µg
1	7.1	128	M	1	18	81.8	77.8	95.5	93.8	85.5	93.1
2	8.4	126	M	1	45	75.5	73.0	82.1	85.4	79.0	88.4
3	14.3	170	M	1	3	53.0	50.4	81.9	81.9	48.6	72.1
4	10.3	145	F	2	16	85.7	83.5	102.7	102.1	75.8	101.9
5	11.8	159	M	1	14	78.9	74.3	104.6	110.4	79.6	102.0
6	12.9	157	M	2	9	59.8	60.1	79.9	84.7	55.2	75.8
7	13.5	167	F	1	4	62.9	65.5	91.3	92.3	67.7	90.6
8	11.8	154	M	1	4	62.9	65.5	91.3	92.3	63.8	93.1
Mean	11.3	151			12†	70.8	69.8	91.1	93.4	69.4	89.6
SD	2.5	17.0				11.6	10.6	9.6	9.6	12.9	10.9

*1—Starting with histamine challenge test; 2—starting with control experiments.
†Geometric mean. ‡Baseline 1—before histamine challenge; baseline 2—70 minutes after histamine challenge.

Figure 2 Mean (SE) FEV_1 (% predicted) from protocol 2 ($n = 8$). Data refer to the control day (closed symbols) and the histamine challenge day (open symbols).



significant differences between baseline 1 and 2 before and after histamine (mean difference 1.0 % predicted, 95% CL -1.7, 3.8) or between baseline on the control day and baseline 1 on the histamine challenge day (mean difference -1.4% predicted, 95% CL -5.3, 2.4) or baseline 2 on the histamine challenge day (mean difference -0.4% predicted, 95% CL -5.3, 4.6). FEV_1 recovered spontaneously within 70 minutes in all children. Administration of 800 μ g salbutamol on the histamine challenge day resulted in an FEV_1 value similar (fig 2) to that on the control day (mean difference -2.0% predicted, 95% CL -5.9, 1.9), with little additional response to the final 200 μ g salbutamol (mean difference -1.2 % predicted, 95% CL -4.1, 1.7). Changes in FEV_1 on the two days were similar, none of the differences reaching statistical significance.

Discussion

This is the first report to address the influence of a histamine provocation test on bronchodilatation after spontaneous recovery from such a challenge. It has been suggested that pulmonary function tests, such as assessment of bronchodilatation, can be performed after a histamine challenge when FEV_1 has returned to 95% of baseline value.⁸ We investigated the effect of a prior histamine challenge on bronchodilatation with salbutamol after spontaneous recovery of FEV_1 order to assess the feasibility of performing the two tests reliably on the same day. Although FEV_1 after 400 μ g salbutamol was significantly diminished by a prior histamine challenge this was not the case after a further 100 μ g had been administered. When 800 μ g salbutamol was inhaled instead of 400 μ g, no effect of a prior histamine challenge was observed. The increase in FEV_1 due to 400 μ g salbutamol was smaller on the histamine challenge day than on the control day when related to pre-histamine FEV_1 , and that trend remained when related to post-histamine FEV_1 . After the further 100 μ g dose the change in FEV_1 as well as the level of FEV_1 appeared to be unaffected by the prior histamine challenge. Similarly, no influence of a prior histamine challenge on FEV_1 or change in FEV_1 was observed after inhalation of 800 μ g salbutamol.

Airways obstruction caused by histamine is a result of a complex process in which airway smooth muscle shortening and oedema¹⁵⁻¹⁷ of

the airway wall due to increased post-capillary venular leakage¹⁸ are thought to be predominant. A thickened mucosa and submucosa and altered volume and properties of airway secretions may affect the availability of the β_2 agonist to the receptor, limiting or delaying the bronchodilator response. Both the time of administration of the β_2 agonist after challenge and the dose of β_2 agonist may therefore influence its response. Some effects of histamine can be antagonised by β_2 agonists, which relax smooth muscle cells and inhibit the release of mediators from mast cells¹⁹; there is no evidence that β_2 agonists reverse airway oedema, though they may prevent its development.²⁰ The influence of β_2 agonists on microvascular leakage and oedema of the airway wall has been studied only in animals, with conflicting reports, the findings varying with the species studied.^{17 21 22}

Results from protocol 1 suggest that after a histamine challenge the same plateau of FEV_1 % predicted is reached as on the control day but it is reached more slowly; this may reflect problems of bronchodilator access to parts of the bronchial tree and subsequent indirect delivery through the bronchial circulation.²³ It is also possible that residual effects of the previous histamine challenge antagonise the response to salbutamol. This could explain why the histamine challenge had no effect on the bronchodilator response when the dose of salbutamol was doubled in the experiments in protocol 2. This is compatible with the observation that incubation of human lung tissue with histamine concentrations greater than 10 μ mol/l induces release of bronchoconstricting ($PGF_{2\alpha}$) and bronchodilating prostaglandins (PGE)²⁴⁻²⁶; these in turn can stimulate mast cells to release bronchodilating and bronchoconstricting prostaglandins.²⁵ Circulating levels of prostaglandins remain raised for over 35 minutes,^{25 27} corresponding with the time airway calibre remains diminished when asthmatic patients inhale these prostaglandins.²⁸ Estimates, on the assumption of an average thickness of the pericellular fluid layer of 5-6 μ m²⁹ and calculated by a method analogous to that used for terbutaline,³⁰ suggest that those in vitro concentrations of histamine are similar to those used in our experiments. Hence mediators released during a histamine challenge may affect the recovery of FEV_1 , and may in part explain why more β_2 agonist is needed even after spontaneous recovery of FEV_1 to obtain the same response as that seen without a prior histamine challenge. Because a maximal effect was obtained a dose higher than the one we used seems unnecessary. After inhalation of this dose of salbutamol we observed a transient tremor in most children, as occurs in adults,³¹ but no other side effects.

We conclude that in children with stable asthma the same level of bronchodilatation, as assessed by FEV_1 , can be achieved with a β_2 agonist, whether or not a prior histamine challenge has been performed. This was achieved with a single 800 μ g dose of salbutamol, administered 70 minutes after the histamine challenge, when FEV_1 has spontaneously returned to baseline. Thus the two tests can be performed on the same day.

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