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 two 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 β₂-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 research; 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 β₂ agonists protect against histamine induced bronchoconstriction for several hours. The effect of a histamine challenge on histamine responsiveness has also been investigated, 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 β₂ agonist even after airway calibre has returned to baseline. Histamine is metabolised within minutes and does not accumulate, provided that several minutes are allowed between inhalations; histamine, however, may reduce air flow for longer. The forced expiratory volume in one second (FEV₁) recoveries within 60 minutes of histamine administration, the recovery time being positively correlated with the dose of inhaled histamine and the magnitude of the response. 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 test 5, 10 litre volume displacement) with a resolution of 20 ml, connected to a computer. The spirometer was heated...
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The best of three technically satisfactory
FEV₁ measurements was recorded¹⁰ and
expressed as percentage of the predicted
value.¹¹

Bronchodilatation was assessed from two
sequential inhalations of salbutamol at 20
minute intervals. A two step administration
of salbutamol was preferred to a single adminis-
tration because it might result in a greater
increase in FEV₁ as a result of better penetra-
tion of the second dose when some broncho-
dilatation 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 diphosphosphate was
inhaled from a calibrated DeVilbiss 646 nebula-
iser 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 his-
tamine solution was delivered to the mouth in
four consecutive breaths. Histamine diphos-
phosphate 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 sal-
butamol was then administered and FEV₁
measured again after 20 minutes. On the his-
tamine 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-
dilatation was measured as on the control day.
Subjects were excluded when complete
recovery was not achieved, or when the base-
line 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 stan-
dard deviation of the reproducibility of
FEV₁ % predicted before bronchodilatation 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-bronco-
dilator 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 dif-
fERENCE −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
Assessment of bronchodilatation after spontaneous recovery from a histamine challenge in asthmatic children

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

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Mean: 10-7 143 32† 79.3 79.4 87.5** 91.5 79.8 91.7 92.2

SD: 1-9 11 7.7 8.5 7.8 8.6 6.7 6.7 7.7

*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).

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

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Mean: 11-3 151 12‡ 70.8 69.8 91.1 93.4 69.4 89.6 92.2

SD: 2-5 17-0

*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.
significant differences between baseline 1 and 2 before and after histamine (mean difference 1-0 % predicted, 95% CI -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% CI -5-3, 2-4) or baseline 2 on the histamine challenge day (mean difference -0-4 % predicted, 95% CI -5-3, 4-6). FEV₁, recovered spontaneously within 70 minutes in all children. Administration of 800 μg salbutamol on the histamine challenge day resulted in an FEV₁ value similar (fig 2) to that on the control day (mean difference -2-0 % predicted, 95% CI -5-9, 1-9), with little additional response to the final 200 μg salbutamol (mean difference -1-2 % predicted, 95% CI -4-1, 1-7). Changes in FEV₁ on the two days were similar, and none of the differences is 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 FEV₁ has returned to 95% of baseline without a method to investigate the effect of a prior histamine challenge on bronchodilatation with salbutamol after spontaneous recovery of FEV₁. In order to assess the feasibility of performing the two tests reliably on the same day. Although FEV₁, after 400 μg salbutamol was significantly diminished by a prior histamine challenge this was not the case after a further 100 μg had been administered. When 800 μg salbutamol was inhaled instead of 400 μg, no effect of a prior histamine challenge was observed. The increase in FEV₁, due to 400 μg salbutamol was smaller on the histamine challenge day than on the control day when related to pre-histamine FEV₁, and that trend remained when related to post-histamine FEV₁. After the further 100 μg dose the change in FEV₁, as well as the level of FEV₁, appeared to be unaffected by the prior histamine challenge. Similarly, no influence of a prior histamine challenge on FEV₁ or change in FEV₁, was observed after inhalation of 800 μg salbutamol. Airways obstruction caused by histamine is a result of a complex process in which airway smooth muscle shortening and oedema is of the airway wall due to increased post-capillary venular leakage are thought to be predominant. A thickened mucosa and submucosa and altered volume and properties of airway secretions may affect the availability of the β₂ agonist to the receptor, limiting or delaying the bronchodilator response. Both the time of administration of the β₂ agonist after challenge and the dose of β₂ agonist may therefore influence its response. Some effects of histamine can be antagonised by β₂ agonists, which relax smooth muscle cells and inhibit the release of mediators from mast cells; there is no evidence that β₂ agonists reverse airway oedema, though they may prevent its development. The influence of β₂ 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.

Results from protocol 1 suggest that after a histamine challenge the same plateau of FEV₁ % 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. 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 microvascular endothelial cells' with concentrations greater than 10 mmol/l induces release of bronchoconstricting (PGF₂α) and bronchodilating prostaglandins (PGÉ₂,PGI₂); these in turn can stimulate mast cells to release bronchodilating and bronchoconstricting prostaglandins. Circulating levels of prostaglandins remain raised for over 35 minutes, corresponding with the time airway calibre remains diminished when asthmatic patients inhale these prostaglandins. Estimates, on the assumption of an average thickness of the cellular fluid layer of 0-5 μm suggest that this concentration of heparin to that used for terbutaline 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 FEV₁, and may in part explain why more β₂ agonist is needed even after spontaneous recovery of FEV₁, 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, but no other side effects.

We conclude that in children with stable asthma the same level of bronchodilatation, as assessed by FEV₁, can be achieved with a β₂ agonist, whether or not a prior histamine challenge has been performed. This was achieved with a single 800 μg dose of salbutamol, administered 70 minutes after the histamine challenge, when FEV₁ has spontaneously returned to baseline. Thus the two tests can be performed on the same day.
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