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

P J F M Merkus, H M Eelkman Rooda, E E M van Essen-Zandvliet, E J Duiverman, Ph H Quanj, K F Kerrebijn

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 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) recovers 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 (Vicistat 5, 10 litre volume displacement) with a resolution of 20 ml, connected to a computer. The spirometer was heated...
to 35-5°C; volumes were corrected to BTPS. The best of three technically satisfactory 
FEV$_1$ measurements was recorded and expressed as percentage of the predicted 
value.

Bronchodilation was assessed from two sequential inhalations of salbutamol at 20 
minute intervals. A two step administration of 
salbutamol was preferred to a single administra-
tion because it might result in a greater 
increase in FEV$_1$, as a result of better penetra-
tion of the second dose when broncho-
dilation has been achieved.

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 
spiration 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 FEV$_1$ was recorded 20 
minutes after each dose of salbutamol. One 
more puff was then inhaled in the same fashion 
and FEV$_1$ was again measured 20 minutes 
later.

Aerosolised histamine diphosphate was inha-
led from a calibrated DeVilbiss 646 nebu-
liser 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/in$^2$). 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.

A total of 20 μl of his-
tamine solution was delivered to the mouth in 
four consecutive breaths. Histamine diphos-
phate in buffered saline was given in doubling 
dilutions (0·25-32 mg/ml). $PD_{20}$ was 
calculated by interpolation of the dose-response 
curve on a log-linear scale.

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 FEV$_1$ 
was followed by four inhalations of 100 μg 
salbutamol and a further measurement of 
FEV$_1$, 20 minutes later. A further 100 μg sal-
butamol was then administered and FEV$_1$ 
measured again after 20 minutes. On the his-
tamine challenge day baseline measurement of 
FEV$_1$ (baseline 1) was followed by a histamine 
challenge test until FEV$_1$ fell by 20%. FEV$_1$ 
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 FEV$_1$, 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 FEV$_1$ measurement on the first day dif-
fereed more than 10% from that on the second 
day.

Protocol 2

The design was the same as in protocol 1, 
extcept 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 
FEV$_1$, after a given dose of salbutamol would 
be the same with as without a prior histamine 
challenge. Post-bronchodilator FEV$_1$% 
predicted and increase in FEV$_1$% 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 dif-
ference in post-bronchodilator FEV$_1$, was 
defined as a difference greater than the stan-
dard deviation of the reproducibility of 
FEV$_1$,% predicted before bronchodilatation in 
asthmatic children. In 78 children with stable 
asthma this was 3·52% predicted, and 
interdependent of the level of FEV$_1$,% predicted, 
age, and sex (own observations). From this it 
can be calculated that 12 subjects would be 
required to detect a difference in post-bron-
chodilator FEV$_1$, 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 FEV$_1$, 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). FEV$_1$, had returned to baseline values 
in 11 children within 60 minutes, and in all 
and after 70 minutes. There were no significant 
differences between baseline 1 and 2 FEV$_1$, 
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 FEV$_1$, 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). 
A further 100 μg salbutamol FEV$_1$, did not 
differ from that on the control day (mean 
difference $-0·7%$ predicted, 95% CL $-3·4, 
2·0$; fig 1). Change in FEV$_1$,% 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

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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).

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.

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 11.6 10-6 9.6 9-6 12.9 10-9 11-0

*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, with no 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 FEV₁ has returned to 95% of baseline. However, we investigated 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 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 tissue with histamine concentration greater than 10 μmol/l induces release of bronchoconstricting (PGF₂α) and bronchodilating prostaglandins (PGE₂). 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 pericellular fluid layer of 5-5 μm, of concentrations greater than 10 μmol/l 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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We thank the participants and the laboratory personnel of the Juliana and Sophia Children’s Hospitals for their contributions to this study. The work was supported by a grant from the Netherlands Health Research Promotion Programme (SGO).

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