Changes in methacholine induced bronchoconstriction with the long acting β_2 agonist salmeterol in mild to moderate asthmatic patients

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Abstract

***Background*—Beta-2 agonists protect against non-specific bronchoconstricting agents such as methacholine, but it has been suggested that the protection afforded by long acting β_2 agonists wanes rapidly with regular treatment.**

***Methods*—The changes in airway responsiveness were investigated during and after eight weeks of regular treatment with salmeterol 50 μg twice daily in 26 adult asthmatic patients, 19 of whom were receiving maintenance inhaled corticosteroids. The study was of a randomised, placebo controlled, double blind design. Airway responsiveness to methacholine was measured as PD_{20} by a standardised dosimeter technique 12 hours after the first dose, at four weeks and eight weeks during treatment (12 hours after the last dose of test medication), and at 60 hours, one week and two weeks after stopping treatment.**

***Results*—There were no significant differences between the baseline characteristics of the two groups. A significant improvement in PD_{20} was seen at all points during treatment with salmeterol compared with the placebo group, with no significant fall off with time. PD_{20} measurements returned to baseline values after cessation of treatment with no significant difference from the placebo group.**

***Conclusions*—Salmeterol gave significant protection against methacholine induced bronchoconstriction 12 hours after administration. This protection was of small magnitude, but there was no significant attenuation with eight weeks of regular use and no rebound increase in airway responsiveness on stopping treatment in a group of moderate asthmatic patients, the majority of whom were receiving inhaled corticosteroids.**

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There is considerable concern that the regular use of β_2 agonists is associated with a deterioration in asthma control and airway responsiveness.[1] The clinical significance of the development of tachyphylaxis to the actions of β_2 agonists in this context remains uncertain. It is known that tachyphylaxis to their systemic effects occurs readily,[2] but studies of tachyphylaxis to their airway actions of bronchodilation and protection against bronchoconstrictor stimuli have produced conflicting results.[3 4]

Salmeterol, a new potent β_2 agonist, has a prolonged duration of action[5] so the risk of developing tachyphylaxis with its regular use may be expected to be higher than with the short acting β_2 agonists. Studies to date have failed to show any tachyphylaxis to its bronchodilator activity.[6] A recent study, however, reported that its protective effect against induced bronchoconstriction may wane with prolonged monotherapy in mild asthmatic patients.[7] The subjects studied, however, had very mild asthma with little or no need for symptomatic relief medication and none had need for prophylactic inhaled steroids.

We have undertaken a placebo controlled study of subjects with mild to moderate asthma, the majority of whom were receiving maintenance inhaled steroid treatment, to assess whether a prolonged course of regular treatment with salmeterol leads to tachyphylaxis of the protective effect against methacholine induced bronchoconstriction at 12 hours after treatment, and exerts any influence on underlying airway responsiveness.

Methods

SUBJECTS

Written informed consent to participate in the study, which had been approved by the Newcastle ethics committee, was obtained from 26 subjects with stable mild to moderate asthma (table 1). All subjects had documented 15% reversibility in peak expiratory flow rate or forced expiratory volume in one second (FEV_1) during the run-in period or in the preceding three months. Nineteen subjects were receiving maintenance inhaled corticosteroids up to a maximum equivalent daily dose of 1000 μg beclomethasone dipropionate together with salbutamol as "rescue" medication. The remaining seven subjects were receiving salbutamol alone on an as required basis. No subject had received oral steroids in the three months leading up to the study.

MEASUREMENTS

A methacholine test was carried out at each

Table 1 Patient characteristics

Subject no	Sex/age	Duration asthma (years)	Daily inhaled steroid dose (μg)	FEV_1 (% pred)	Geometric mean baseline PD_{20} (μg)
Salmeterol group					
1	F/54	40	200	76·3	16·5
2	F/50	5	0	106·9	932·6
3	F/22	5	200	92·3	6·3
4	F/44	0·5	1000	76·8	174·6
5	F/49	13	200	82·3	9·5
6	M/40	39	400	70·0	24·4
7	F/55	5	800	73·0	10·1
8	M/34	6	400	74·7	26·0
9	M/50	40	0	56·0	6·7
10	M/26	25	0	120·8	161·9
11*	F/22	17	0	88·8	7·0
12**	F/20	9	400	103·5	7·1
13**	M/21	20	0	95·7	61·6
Placebo group					
14	M/40	35	1000	89·1	158·4
15	M/42	5	1000	73·6	18·9
16	F/64	18	200	68·7	31·6
17	M/33	33	400	106·5	77·2
18	F/43	3	500	99·2	19·4
19	F/55	30	800	74·6	15·5
20	F/36	35	100	102·8	16·5
21	M/41	20	0	84·3	14·7
22	F/29	2·5	800	107·3	1248·8
23	M/19	2·5	0	97·8	2246·5
24	F/36	15	1000	65·5	8·8
25	F/63	4	1000	72·7	10·6
26**	F/19	19	400	75·9	18·0

*Withdrawn because of exacerbation of asthma; **withdrawn from study (see text).

visit using a standard dosimeter technique as described previously.[8] Briefly, after three sets of baseline FEV_1 measurements, subjects inhaled five breaths per dose from sequential doubling concentrations of methacholine solution at five minute intervals. Doses ranged from 3·125 μg to a maximum of 6400 μg. Aerosol was generated by a compressed air driven turbo jet nebuliser (Medic Aid, Pagham, UK) controlled by a breath activated dosimeter. Nebuliser output was calibrated to deliver 10 μl (±10%) of aerosol per breath. FEV_1 measurements were made using a Jaeger "Screenmate" pneumotachometer (Erich Jaeger UK Ltd, Market Harborough, UK), taking the mean of the best three of six manoeuvres. The methacholine test was completed when a 20% decrement in FEV_1 was attained or when the maximum cumulative dose of 6400 μg of methacholine had been given. FEV_1 was plotted against log cumulative dose to obtain the methacholine PD_{20} value by linear interpolation.

Table 2 Mean (SE) lung function and geometric mean (SE) methacholine PD_{20} results

	Salmeterol (n = 10)		Placebo (n = 12)	
	FEV_1 (% pred)	PD_{20} (μg)	FEV_1 (% pred)	PD_{20} (μg)
Baseline	82·9 (6)	32·0 (1·7)	86·8 (5)	47·7 (1·7)
Treatment period				
+12 hours	87·8 (5)	59·8 (1·8)	85·2 (4)	37·8 (1·7)
+4 weeks	82·1 (5)	71·8 (1·9)	84·2 (4)	48·3 (1·7)
+8 weeks	82·9 (7)	52·0 (2·0)	87·8 (5)	45·3 (1·6)
Post treatment period				
+60 hours	80·6 (5)	39·6 (1·9)	88·2 (5)	50·0 (1·8)
+1 week	81·7 (6)	37·5 (1·8)	86·9 (5)	55·5 (1·8)
+2 weeks	80·7 (6)	46·0 (2·0)	89·1 (5)	61·7 (1·8)

STUDY DESIGN

A double blind placebo controlled parallel design was used. Subjects had two baseline visits within 12 days of each other and at least 48 hours apart to ensure that there was no refractoriness to methacholine to confound results.[9] They were then randomised to receive salmeterol 50 μg twice daily or matching placebo by metered dose inhaler (MDI). Methacholine tests were carried out 12 hours after the first dose and again after four and eight weeks of treatment. These tests were conducted at the same time of day and 12 hours after the last MDI treatment. Study treatments were stopped at eight weeks and further methacholine tests were performed 60 hours, one week, and two weeks later, again at the same time of day.

Subjects were allowed to use salbutamol as "rescue medication" but none was taken for at least eight hours before a methacholine test. The study was performed out of the grass pollen allergy season.

STATISTICAL ANALYSIS

All PD_{20} values were $\log_{10}$ transformed before analysis. Changes in PD_{20} from mean baseline values were expressed in terms of doubling doses of methacholine calculated as $\Delta\log PD_{20}/\log 2$.

Results were analysed by repeated measures analysis of variance (MANOVA) using the SAS statistical package which took into account individual variations with time and between treatments; p values $<0{\cdot}05$ were considered significant.

The coefficient of repeatability for airway responsiveness measurements was calculated using the two baseline visits for each subject.[10]

Results

Four patients dropped out of the study after four weeks of treatment, three of whom had been randomised to receive salmeterol. Reasons for withdrawal were: shigella dysentery, exacerbation of asthma requiring oral steroids, and social circumstances. The fourth patient was in the placebo group and was non-compliant with treatment. Their results were excluded from the analysis.

BASELINE DETAILS

There were no significant differences between the salmeterol and placebo groups with respect to age, sex, smoking history, mean baseline FEV_1, or airway responsiveness. The coefficient of repeatability overall for baseline airway responsiveness measurements was 0·66 doubling doses of methacholine. There were no differences between the groups.

LUNG FUNCTION

There were no significant differences between the two groups in FEV_1 values before methacholine challenge, during the treatment phase or after stopping (table 2).

METHACHOLINE CHALLENGE TESTS

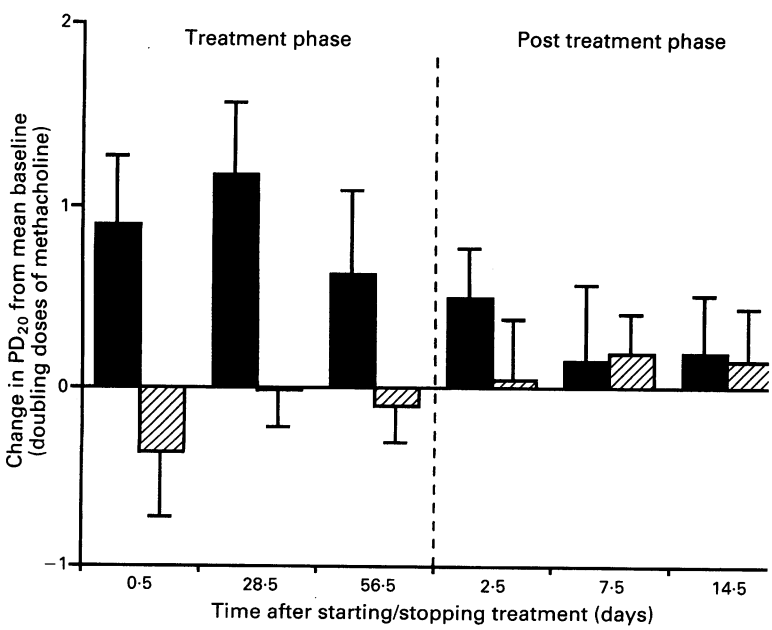
PD_{20} measurements were significantly higher throughout the treatment period with salmeterol than with placebo, $p = 0{\cdot}01$ (figure). This protective effect against methacholine induced bronchoconstriction was seen after the first dose of salmeterol and was maintained without significant change throughout the treatment period, although PD_{20} measurements on day 56 tended to be slightly lower.

On stopping salmeterol, PD_{20} measurements returned rapidly to baseline values. There were no significant differences when compared with the placebo group at 60 hours, one week or two weeks after cessation of treatment, although there was a suggestion of some residual protection at 60 hours.

Discussion

This study has shown that salmeterol gives significant protection against methacholine induced bronchoconstriction 12 hours after the first dose compared with placebo. This protective effect is of small magnitude but is maintained during the eight weeks of active treatment with no significant attenuation. After cessation of salmeterol, airway responsiveness returns rapidly to baseline levels with no evidence of a rebound increase.

That no airway tachyphylaxis was shown in this study is in contrast to a recent study by Cheung *et al*,[7] although the designs of the two studies were different. In our study there was no interruption of the regular 12 hourly medication, airway responsiveness being measured just before the next scheduled dose. This is perhaps more reflective of its clinical use. Similarly, if significant attenuation of the protective effect of salmeterol on methacholine induced bronchoconstriction were to develop it might be expected to be more evident at the extreme end of its action—that is, at 12 hours after the last regular dose rather than at one hour after the test dose and after a washout as used by Cheung *et al*.[7]



Mean (SE) change in airway responsiveness from baseline in doubling doses of methacholine during and after eight weeks of treatment with salmeterol (■) or placebo (▨).

One other reason for the discordant results may be differences in the susceptibilities of subjects with different asthma severity to the development of tachyphylaxis. Indeed, some studies have shown that it is easier to induce tachyphylaxis in normal subjects than in asthmatic subjects.[11] Although a mixed group, our patients all had need of relief bronchodilator treatment and 73% required prophylactic inhaled steroids for asthma control. This contrasts with the patient group studied by Cheung *et al*,[7] many of whom were not even receiving relief medication.

Corticosteroids themselves are known to have a "permissive" or facilitating effect on catecholamine function and have been shown to reverse the tachyphylaxis induced in normal volunteers to high dose inhaled salbutamol.[12] That significant airway tachyphylaxis did not develop in our study may be due to the use of inhaled corticosteroids. It remains possible that tachyphylaxis was merely delayed by corticosteroid usage, and it will be important to conduct further studies over a longer treatment period. It is now recommended that patients who require regular inhaled bronchodilator treatment should receive inhaled corticosteroids.[13] We would suggest that this might be advisable, not only to treat the underlying airway inflammation but also to minimise the risk of developing airway tachyphylaxis.

Our inability to show significant airway tachyphylaxis in this study may have been a consequence of the small sample size. The study did, however, have a 60% power to detect a doubling change in PD_{20}.

The clinical significance of the protection afforded by β_2 agonists to methacholine induced bronchoconstriction is difficult to evaluate. The mean protection afforded by salmeterol at 12 hours in our study was small, ranging from 0·6 to 1·2 doubling doses of methacholine. This is slightly lower than the 2–3 doubling dilutions reported in other studies.[5,14] This may reflect, firstly, that tachyphylaxis had already developed as a result of prior frequent use of "rescue" β_2 agonists. Whether this occurs with short acting β_2 agonists is controversial, being described in some[4] but not other[3] studies. Secondly, we did not have any residual bronchodilation at 12 hours which seems to be a confounder in some studies.[15] This was the case even at the beginning of the study and does not itself represent tachyphylaxis to salmeterol. It is more likely to be a feature of this group of patients with more severe disease.

The protection afforded by salmeterol was short lived, and was not significantly different from placebo 60 hours after the last dose. Importantly, however, there was no deterioration in airway responsiveness below baseline values at 60 hours, one week, or two weeks after stopping treatment. This is in agreement with the study by Cheung *et al*[7] and a previous study by our group[16] which found no change in airway responsiveness at 24 hours, 72 hours, and two weeks after stopping six weeks of regular salmeterol or salbutamol.

A rebound increase in airway responsiveness may have been missed if it occurred at time points when methacholine testing was not performed. In the study by Vathenan *et al*[17] which suggested a rebound effect after stopping terbutaline, the maximum difference in measurements of airway responsiveness between terbutaline and placebo groups on cessation of treatment occurred at 23 hours after the last dose—that is, six times the half life of terbutaline. We made measurements at 12 hours and 60 hours after the last dose (5·5 times the half life of salmeterol). These time points were chosen to allow 48 hours between measurements to avoid the confounding problems of refractoriness to methacholine.[9] It therefore seems unlikely that any significant rebound increase in airway responsiveness occurs after salmeterol use.

In conclusion, our study was designed to be relevant to the present clinical use of salmeterol. The results of the present study were, therefore, reassuring. We found no evidence of airway tachyphylaxis during eight weeks of regular salmeterol treatment, nor a rebound increase in airway responsiveness on stopping treatment, in a group of patients with mild to moderate asthma.

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