

Regular inhaled β agonist in asthma: effects on exacerbations and lung function

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Abstract

Background A comparison of the effects of regular *v* as needed inhaled β agonist treatment on the control of asthma in the last 16 weeks of each of two 24 week treatment periods has been reported. This paper presents additional information on exacerbations of asthma and trends in lung function, airways hyperresponsiveness to methacholine, and bronchodilator responsiveness during the entire 24 week periods of regular or as needed β agonist treatment.

Methods Subjects undertook a year long randomised, double blind crossover study of regular *v* as needed inhaled β agonist treatment. Fenoterol (400 μ g) or matching placebo was inhaled as a dry powder four times daily for 24 weeks, then subjects crossed over to the alternative regimen. Treatment with inhaled corticosteroids was used by 50 of the 64 subjects in constant doses throughout the study. Symptoms, peak expiratory flow rates, and drug use were recorded daily, spirometry was performed every four weeks, and methacholine and bronchodilator responsiveness were measured every eight weeks.

Results Exacerbations of asthma symptoms occurred earlier and more often during regular treatment with fenoterol and four of five severe exacerbations requiring admission to hospital occurred during the period of regular treatment. Prebronchodilator forced expiratory volume in one second (FEV₁) was on average 0.15 litres lower (95% confidence interval (95% CI) 0.11-0.19) and vital capacity (VC) 0.12 litres lower (95% CI 0.08-0.16) than during the placebo period. Morning peak flow rates were significantly lower and evening peak flow rates significantly higher, with an increase in diurnal variation from 9.8% (95% CI 6.9-12.8) to 17.5% (95% CI 13.8-21.3) during regular treatment. Geometric mean concentration of methacholine causing a 20% fall in FEV₁ from the value after saline (PC₂₀) decreased significantly from 1.63 to 1.15 mg/ml, indicating increased bronchial hyperresponsiveness during regular treatment. Response to bronchodilator, as measured by the % increase in post-bronchodilator FEV₁ related to prebronchodilator FEV₁, was maintained with no evidence for tachyphylaxis.

Conclusion Chronic use of inhaled

fenoterol resulted in more exacerbations, a significant decline in baseline lung function, and an increase in airway responsiveness to methacholine in asthmatic subjects, but did not alter bronchodilator responsiveness. These findings support the previous report that regular inhaled β agonist treatment is deleterious in the long term control of asthma.

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Although inhaled β agonists provide rapid relief of symptoms of asthma, some studies have suggested that regular use of an inhaled β agonist drug may cause a decrease in lung function,^{1,2} an increase in reactivity to non-specific bronchoconstrictors such as methacholine,^{3,4} and rebound airway responsiveness on cessation of β agonist treatment.⁵ Other studies have questioned whether chronic β agonist treatment may induce tachyphylaxis and reduce the bronchodilator response to supplementary treatment.⁶⁻⁸ We recently reported that the clinical control of bronchial asthma was made worse by regular inhalation of the β agonist fenoterol bromide.⁹ This paper reports further data from that study related to the clinical course of patients over the full treatment period, including the number and severity of exacerbations, and describes the changes in lung function and in methacholine and bronchodilator responsiveness with time.

Methods

Details of the trial design, subjects, and methods have been reported.⁹ Briefly, 64 adults (table 1) who had had mild to moderate asthma (not requiring continuous oral corticosteroid treatment) for at least one year

Table 1 Anthropometric data for 64 study subjects

Subjects	28 male, 36 female
Age (y)	Range 15-64, median 38, mean 37.2
Smoking state (No):	
Non-smokers	42 (66%)
Ex-smokers	19 (30%)
Current smokers	3 (5%)
FEV ₁ (l) at entry	2.46 (95% CI 2.25-2.67) 77.0% predicted (95% CI 73.1-80.9)
Daily inhaled corticosteroid dose (No)	
Nil	14
150-400 μ g	24
401-800 μ g	15
>800 μ g	11

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completed a double blind, randomised, placebo controlled cross over study in which for two periods of 24 weeks each, either fenoterol bromide (400 μg) or matching placebo was inhaled as a dry powder four times daily. This dose was equivalent to the usual dose of fenoterol given by metered dose inhaler (200 μg , two puffs four times a day) in New Zealand at that time. Subjects were allowed additional known β agonist (fenoterol (29 subjects), salbutamol (33 subjects), or terbutaline (two subjects)) by metered dose inhaler for relief of symptoms as needed.⁹ All other bronchodilators (oral β agonists, theophylline, inhaled ipratropium) were required to be withdrawn before entry without compromising lung function. Inhaled corticosteroid was used by 50 of the 64 subjects (dose range 150 to 3000 μg , median 600 μg , mean 803 μg) and had been taken in a stable dose for at least three months before the study began; many subjects had used inhaled corticosteroids for years. No change in the maintenance dose was permitted even during exacerbations, which were treated with known β agonist by metered dose inhaler as required and, if more severe, by a short standardised course of oral prednisone.⁹

Control of asthma was assessed from daily symptom scores, morning and evening peak flow rates measured by mini-Wright meter, the need for additional inhaled β agonist, and for short courses of prednisone. The onset of an exacerbation of asthma was defined as the day of concurrent appearance of two or more of the predetermined criteria listed in table 2. The duration of an exacerbation was calculated as the days from the onset until symptom scores and peak flow rates returned to the previous baseline. When a return to previous baseline was not achieved, the exacerbation was assumed to have ended when a new stable baseline appeared.

Every four weeks subjects performed spirometry; this was followed by either a methacholine or bronchodilator challenge. The best of at least three acceptable (to within 5%) vital capacity (VC) and forced expiratory volume in one second (FEV_1) measurements on a Godart water spirometer were recorded. Methacholine challenge was performed on alternate four-weekly visits by the method of Cockcroft *et al.*¹⁰ Bronchodilator responsiveness was assessed on alternate visits by repeating spirometry 10 minutes after administration of nebulised salbutamol (5 mg/ml) or fenoterol (5 mg/ml)

for two minutes. The drug used for each bronchodilator challenge in individual patients was that in the known metered dose inhaler β agonist used by that patient. Nebulised β agonist was delivered by a Hudson up-draft nebuliser with oxygen at a flow rate of 6 l/min delivering 0.13 ml/min; this provided a delivered dose of about 1.25 mg of either agent. Subjects refrained from using any treatment with inhaled drugs (including the blinded trial medication) for at least six hours before attending the laboratory.

STATISTICAL ANALYSIS

Observed FEV_1 and VC were compared with predicted values determined for age, sex, and height from formulae for New Zealand caucasians previously reported from our laboratory.¹¹ Mean morning and evening peak expiratory flow rates were calculated for each successive four week period. Diurnal variation in peak flow was calculated from the formula:

$$[(\text{evening-morning PEF})/\text{evening PEF}] \times 100\%$$

Airway responsiveness was measured as the provoking concentration of methacholine ($\text{PC}_{20} \text{FEV}_1$) that caused a 20% fall in FEV_1 from the value after saline.¹⁰ The PC_{20} values were log transformed for comparisons. Response to bronchodilator was measured as the increment in FEV_1 expressed as % of the prebronchodilator FEV_1 :

$$[(\text{postbronchodilator } \text{FEV}_1 - \text{prebronchodilator } \text{FEV}_1) / \text{prebronchodilator } \text{FEV}_1] \times 100\%.$$

Data were analysed with the SSPSX:MANOVA procedure for analysis of variance of repeated measurements,¹² to identify between treatment differences and treatment-time interactions. Paired survival analysis by the method of Akrits was used to determine the significance of differences in exacerbation rates between treatments.¹³

Results

Despite instruction not to vary inhaled corticosteroid dose throughout the study, diaries from 11 subjects showed differences in cumulative consumption of inhaled corticosteroid between treatment periods of greater than 5%. Nine of these 11 used more inhaled corticosteroid during the period of active fenoterol treatment. Any bias from this increase in dose should favour a better outcome on regular treatment, but in fact there were more exacerbations of asthma and indices of lung function were lower during regular fenoterol treatment.

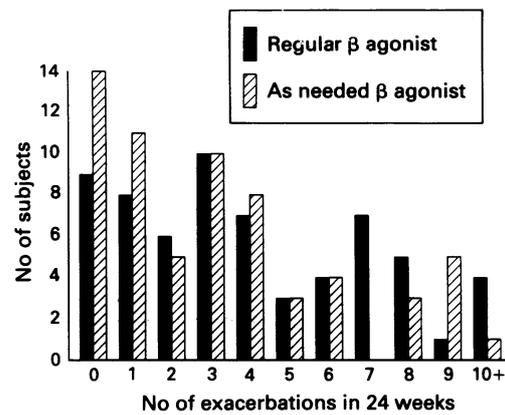
Figure 1 shows the number of exacerbations experienced by each subject during each 24 week treatment period. Almost twice as many subjects experienced more than six exacerbations during regular treatment compared with during as needed treatment (17 v nine subjects). On the other hand, 25 subjects had no, or only one exacerbation during as needed treatment compared with only 17 during regular treatment. There were 261 exacerbations (mean 4.1 per subject) during

Table 2 Criteria for an exacerbation

An exacerbation was recorded when there was concurrent development of two or more of the criteria:

- 1 (a) Appearance of nocturnal cough or wheeze, or
(b) worsening of usual nocturnal cough or wheeze
- 2 Fall in morning PEF to <70% usual value
- 3 Increase in need for additional bronchodilator to >6 puffs/day greater than usual
- 4 (a) Development of cough and sputum or
(b) increase in usual symptoms of cough and sputum
- 5 Increase in dyspnoea sufficient to limit activities
- 6 (a) Need to commence oral corticosteroids or
(b) increase in dose of oral corticosteroids

Figure 1 Number of exacerbations experienced by each subject during each treatment period.



regular treatment, compared with 201 (mean 3.1 per subject) during as needed treatment. Overall, 36 subjects (56%) had more exacerbations during treatment with regular β agonist compared with 20 subjects (31%) with more exacerbations during as needed treatment. These differences in exacerbations between treatment periods did not reach statistical significance.

The median time from the commencement of each treatment period to the first exacerbation was 33 days when on regular treatment compared with 66 days when taking β agonist only as needed ($t = 2.39$, $df = 63$, $p = 0.02$). Separation of the "survival curves" was seen after two weeks (fig 2). At 30 days, 31 subjects had experienced an exacerbation while on regular β agonist, compared with 19 on as needed treatment. After 90 days of regular treatment, 51 subjects had had an exacerbation compared with 37 during as needed treatment.

Severe exacerbations requiring admission to hospital occurred in five patients and of these, four occurred during regular fenoterol treatment. All occurred after at least 16 weeks of treatment.

Twenty three subjects required one or more short courses of prednisone during the study. Seventeen patients required prednisone during regular treatment (mean duration 30 days, 95% confidence interval (95% CI) 11–49), and 14 during placebo (mean 24 days, 95% CI 11–37); eight of these used

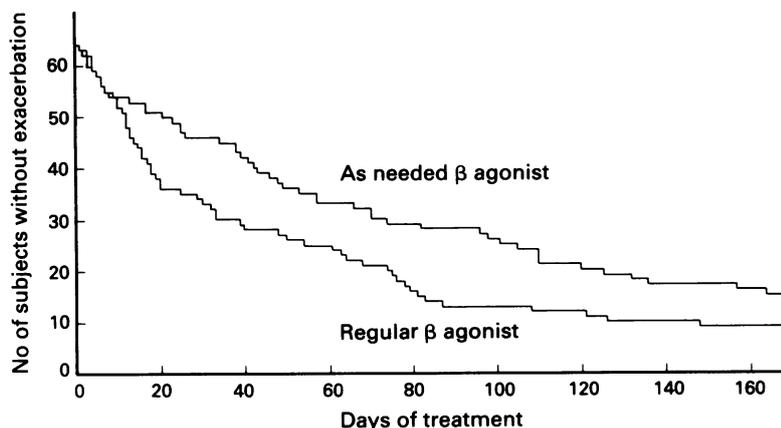


Figure 2 "Survival curve" of subjects not experiencing an exacerbation by duration of treatment period.

Table 3 Mean FEV₁ (l) for 64 subjects during regular and as needed β agonist treatment

Week	Regular β agonist Mean (95% CI)	As needed β agonist Mean (95% CI)	Difference
0	2.41 (2.21–2.61)	2.45 (2.23–2.67)	0.04
4	2.38 (2.10–2.66)	2.49 (2.22–2.76)	0.11
8	2.33 (2.12–2.54)	2.62 (2.36–2.88)	0.29
12	2.38 (2.09–2.67)	2.48 (2.27–2.69)	0.09
16	2.33 (2.14–2.52)	2.45 (2.24–2.66)	0.12
20	2.35 (2.15–2.55)	2.46 (2.26–2.66)	0.11
24	2.30 (2.09–2.51)	2.46 (2.26–2.66)	0.17
Mean difference			0.15

$p < 0.005$ for difference in treatment effect on absolute FEV₁.

prednisone during both periods. These differences in use of prednisone were not statistically significant. Significant individual between treatment differences in use of prednisone occurred, however, in 19 patients, of whom 11 required more prednisone during regular β agonist treatment.

Mean prebronchodilator FEV₁ was significantly lower (0.15 l, $p < 0.005$) at all time points during regular fenoterol treatment compared with as needed treatment (table 3). There was no time treatment interaction—that is, FEV₁ was lower during regular treatment but did not deteriorate further after the first four weeks of treatment. Vital capacity was also significantly lower (0.12 l, $p < 0.01$), during regular treatment. There was a significant time-treatment interaction on VC during both regimens ($p < 0.001$), but the slight downward slope did not differ between regimens ($p = 0.33$).

Table 4 shows the increases in FEV₁ after nebulised bronchodilator at baseline and at eight week intervals throughout the study. Differences in response between treatments were not significant.

Figure 3 shows mean morning and evening peak flow rates calculated for each four-week interval during the study. Morning peak flow rates were consistently higher during the period of as needed bronchodilator treatment ($p < 0.003$). There was no significant change with time after week eight. Evening peak flow rates were significantly higher during treatment with regular fenoterol ($p < 0.0005$); this effect was noted immediately. The overall mean morning peak flow was 402 l/min during as needed treatment compared with 392 l/min during regular treatment. The evening values were 432 l/min and 446 l/min respectively. The slight downward trends in peak flows with time during regular treatment and

Table 4 Bronchodilator responsiveness expressed as increase in FEV₁ as % prebronchodilator FEV₁ by treatment regimen

Week	Regular β agonist Mean (95% CI)	As needed β agonist Mean (95% CI)
0	29.3 (23.5–35.1)	27.0 (20.3–33.7)
4	30.9 (23.8–38.0)	27.5 (21.6–33.4)
12	30.1 (23.4–36.9)	26.7 (21.7–31.7)
20	26.6 (21.4–31.8)	27.3 (22.1–32.4)

Differences between treatments are not significant.

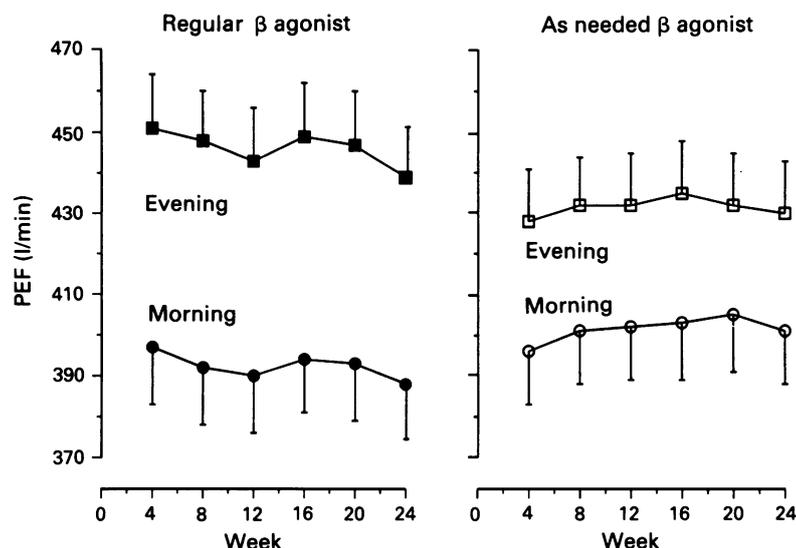


Figure 3 Mean morning and evening peak flow rates (with standard error bars) during regular and as needed β agonist treatment, averaged over each four week period.

slight upward trends during as needed treatment (fig 3) were not statistically significant. The diurnal variation in peak flow rate increased significantly from 9.8% (95% CI 6.9–12.8) during as needed bronchodilator treatment to 17.5% (95% CI 13.8–21.3) during regular bronchodilator treatment ($p < 0.0005$).

Table 5 gives the geometric mean data for measurements of airway responsiveness at baseline and at weeks eight, 16, and 24 of each treatment period. Geometric mean PC_{20} , although variable, was consistently lower during regular β agonist treatment (airway responsiveness was greater). Although the overall mean PC_{20} was only a half concentration lower during regular treatment (1.15 compared with 1.63 mg/ml during as needed treatment), the difference at each period was highly significant ($p = 0.003$). There was no significant time trend ($p = 0.12$).

Discussion

These results supplement those reported earlier,⁹ and are consistent with the conclusion that control of bronchial asthma is worse when a β agonist bronchodilator is inhaled regularly. In our earlier report, assessment was based on intraindividual comparisons of markers of asthma control in the last 16

weeks of each treatment period after allowing an eight-week washout period. In this paper clinical and physiological measurements are analysed as mean group data for the entire 24 weeks of each period.

It proved difficult to precisely quantify the duration of asthma exacerbations in this study, despite the prospective use of predetermined criteria. Whereas the onset of an exacerbation was readily determined, the end was less clear, especially if a return to former baseline measurements of morning peak flow or symptom state was not achieved. If the baseline state deteriorated, then the time for recovery after an exacerbation to a new (worse) baseline would be shorter than if the episode were recorded as persisting until the original baseline values were recovered. In some instances this would never have been achieved. Hence we may have underestimated the duration of some exacerbations, particularly during regular treatment when baseline shifts were more evident, as seen in the pulmonary function data. Despite this, we found that more subjects experienced more exacerbations during the period of regular fenoterol treatment, and the median time to the first exacerbation was significantly shortened during regular treatment compared with as needed treatment.

The decreases in prebronchodilator FEV_1 and in morning peak expiratory flow rates, together with the increase in diurnal variation of peak flow rates, were all highly significant. Increased diurnal variation was attributable in part to the acute bronchodilator effect during the period of regular treatment giving an increased evening peak flow rate, and also to a consistently lower morning peak flow rate during regular treatment. This suggests that, when the acute bronchodilator action of fenoterol waned, baseline bronchoconstriction increased.

This phenomenon of rebound bronchoconstriction (that may in part explain the overall adverse effect of regular treatment with bronchodilator) has been found previously in association with the use of high doses of isoprenaline.^{14,15} Rebound bronchoconstriction may also explain why subjects found it necessary to continue to use supplementary bronchodilator during fenoterol treatment (mean 2.45 puffs per day, (95% CI 2.15–2.75)). The retention of a normal response to acute administration of β agonist may explain why patients and physicians alike have not recognised the adverse effects of chronic β agonist treatment. As measured by a conventional reversibility test, there was no evidence of tachyphylaxis. Likewise the relevance of the small decline in prebronchodilator FEV_1 is unlikely to be recognised if postbronchodilator values are undiminished.

Decreases in lung function during regular treatment with fenoterol have been reported by others. Trembath *et al*¹⁶ showed that FEV_1 fell from a mean value of 2.76 to 2.43 litres ($p < 0.05$) in 15 asthmatic subjects treated with inhaled fenoterol for four weeks. Van Arsdell *et al*¹⁷ recorded a fall in FEV_1 from

Table 5 Airway responsiveness to methacholine by time and treatment regimen

Week	Regular β agonist Mean* (95% CI)	As needed β agonist Mean* (95% CI)
0	1.19 (0.87–1.63)	1.34 (1.01–1.77)
8	0.98 (0.70–1.37)	1.48 (1.02–2.15)
16	1.05 (0.73–1.51)	1.46 (0.95–2.24)
24	1.46 (1.09–1.96)	2.00 (1.45–2.75)
Overall	1.15	1.63

*Geometric mean. Differences in PC_{20} between treatments highly significant ($p = 0.003$) at each interval.

2.53 to 2.05 litres in 13 subjects treated for 12 weeks with oral fenoterol. Such effects have also been found using β agonists other than fenoterol. Harvey and Tattersfield gave atopic non-asthmatic and atopic asthmatic subjects inhaled salbutamol in increasing doses from 100 μg four times daily in week 1 to 500 μg qid in week 4.¹ There were significant falls in FEV₁ of 0.35 litres in the asthmatic group, and 0.24 litres in the non-asthmatic group. More recently, use of regularly inhaled salbutamol by asthmatic patients for four months was associated with a significant ($p < 0.0001$) fall in FEV₁ from 79% to 76% predicted.¹⁸

This study confirms previous reports that regular β agonist treatment results in a small but significant increase in airway responsiveness to non-specific challenge.^{3,4} Van Schayck and colleagues found a similar significant reduction in PC₂₀ in subjects with chronic bronchitis or asthma given regular salbutamol for one year.³ In shorter studies, both Kraan *et al*⁴ and Kerrebijn *et al*¹⁹ found that methacholine or histamine responsiveness increased slightly during regular terbutaline treatment by contrast with the decreased responsiveness seen during regular inhaled corticosteroid treatment.

The changes in airway responsiveness that occur with regular β agonist treatment are small, and are considerably less than the two to fourfold reductions in responsiveness that have been described during inhaled corticosteroid treatment.^{20,21} Nevertheless, increased airway responsiveness is a consistent finding irrespective of the β agonist used. Although the magnitude of these changes in PC₂₀ and FEV₁ may seem to be small and of little significance in any one patient, they are highly significant in populations of asthmatic patients. The epidemiological impact of such changes has been discussed by Mitchell,²² who argued how a small shift in mean PC₂₀ for an asthmatic population (whether due to regular β agonist treatment or to other causes) could explain an increase in the prevalence of more severe disease, and the gradually worsening morbidity and mortality from asthma evident worldwide.^{23,24}

In summary, the occurrences of exacerbations and changes in lung function and non-specific airway responsiveness that we have recorded during 24 weeks of treatment with regular fenoterol compared with placebo are consistent with physiological changes identified in other investigations, and correlate with the deterioration in overall control of bronchial asthma that we previously reported.⁹ These findings reinforce recommendations that short acting β agonists should not be used for regular maintenance treatment in asthma. At the very least, they add to a growing body of evidence indicating that regular long term treatment with inhaled bronchodilators confers no significant benefit on lung function, and may in fact be deleterious.

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