Reversing acute bronchoconstriction in asthma: the effect of bronchodilator tolerance after treatment with formoterol


ABSTRACT: Continuous treatment with a short-acting β2-agonist can lead to reduced bronchodilator responsiveness during acute bronchoconstriction. This study evaluated bronchodilator tolerance to salbutamol following regular treatment with a long-acting β2-agonist, formoterol. The modifying effect of intravenous corticosteroid was also studied.

Ten asthmatic subjects (using inhaled steroids) participated in a randomised, double-blind, placebo-controlled, cross-over study. Formoterol 12 μg b.i.d. or matching placebo was given for 10–14 days with > 2 weeks washout. Following each treatment, patients underwent a methacholine challenge to induce a fall in forced expired volume in one second (FEV1) of at least 20%, then salbutamol 100 μg, 100 μg, and 200 μg was inhaled via a spacer at 5 min intervals, with a further 400 μg at 45 min. After a third single-blind formoterol treatment period, hydrocortisone 200 mg was given intravenously prior to salbutamol. Dose-response curves for change in FEV1 with salbutamol were compared using analysis of covariance to take account of methacholine-induced changes in spirometry.

Regular formoterol resulted in a significantly lower FEV1 after salbutamol at each time point compared to placebo (p < 0.01). The area under the curves (AUCs) for 15 (AUC0–15) and 45 (AUC0–45) min were 28.8% and 29.5% lower following formoterol treatment (p < 0.001). Pretreatment with hydrocortisone had no significant modifying effect within 2 h of administration.

It is concluded that significant tolerance to the bronchodilator effects of inhaled salbutamol occurs 36 h after stopping the regular administration of formoterol. This bronchodilator tolerance is evident in circumstances of acute bronchoconstriction.


Current guidelines for the management of chronic asthma propose that long-acting β-agonists such as salmeterol and formoterol should be added to anti-inflammatory treatment for the control of persistent or breakthrough symptoms [1, 2]. This strategy appears to be beneficial not only in controlling symptoms [3–7], but also in reducing the frequency of asthma exacerbations during long-term treatment [8, 9].

Despite these positive outcomes, against a background of concern about the safety of β-agonists [10] significant attention has been given to the issue of β-adrenoceptor down-regulation and the advent of drug tolerance. A number of studies using salmeterol and formoterol have been conducted to investigate this issue. These have shown that during treatment with long-acting agents, tolerance to the protective effects of β-agonists against exercise-induced bronchospasm [11] and nonspecific bronchoconstrictors is easily demonstrated [12] and develops rapidly [13]. Concurrent treatment with inhaled corticosteroid does not appear to modify these effects [14–17], although corticosteroids may be used acutely to reverse them [18, 19].

In contrast, evidence for the development of bronchodilator tolerance has been less clear cut. In the majority of studies, no evidence of impaired bronchodilator responsiveness has been found [20–24], although in some investigations a reduction in bronchodilator response has been reported [18, 25, 26]. However, a major drawback in the design of these studies is that most have been carried out in patients with stable asthma, in whom a reduction in β2-adrenoceptor function may be relatively unimportant in maintaining adequate bronchomotor tone. This contrasts with patients with acute asthma.

Recently, using a simple but novel approach, the authors have demonstrated that after six weeks regular treatment with the short-acting β2-agonist terbutaline, the bronchodilator response to salbutamol is significantly reduced in circumstances of acute bronchoconstriction [27]. This is more relevant in determining the clinical importance of tolerance. The present study has extended this approach to assess the development of bronchodilator tolerance during regular treatment with the long-acting β-agonist formoterol. The study was
also designed to confirm whether administering systemic corticosteroid rapidly reverses any observed effect.

**Methods**

**Subjects**

Volunteers aged 18–70 yrs, with a history of mild to moderate asthma, were invited to participate in the study. All had a positive methacholine challenge (provocative dose causing a 20% fall in forced expiratory volume in 1 second (FEV1) of less than 8 µmol (PD20)) within 2 months of recruitment. All were receiving maintenance inhaled corticosteroid treatment with no change in dose or other asthma treatment during the 6 weeks prior to enrolment. All those receiving oral or high dose inhaled corticosteroids were excluded, as were patients receiving maintenance inhaled long-acting β2-agonists. Current or previously heavy cigarette (>5 pack years) smokers were also excluded.

**Study design**

All patients entered a 2-week run-in phase during which control of asthma was assessed by means of a daily record card in which patients entered morning and evening peak flows and symptom scores. Throughout the study patients were maintained on their usual dose of inhaled steroids. All β2-agonists were stopped and patients were provided with ipratropium bromide 40 µg puff (Boehringer, Ingelheim, Germany) for "as required" use. Patients with unstable asthma, or who were unable to obtain adequate relief of breakthrough symptoms using inhaled ipratropium bromide during the run-in, were withdrawn from the study. All other patients then received each of the first two study treatments according to a randomised, double-blind, crossover design. The treatments were formoterol (Foradil, Novartis, Basel, Switzerland) 12 µg twice daily administered as dry powder via an aeroliser for 7–10 days, and matching placebo containing lactose. There was a washout period of at least 2 weeks between each of the first two treatments. Following a further 2 week washout interval, patients proceeded into a third treatment period during which formoterol 12 µg daily was administered single-blind (patient) for 7–10 days. This was to permit a subsequent assessment of the effect of intravenous hydrocortisone on the bronchodilator dose-response.

**Study visits and measurements**

Patients visited the research laboratory at the completion of each of the three treatment periods. Study medications and inhaled ipratropium were withheld for at least 36 and 6 h respectively. On each occasion, and prior to any measurements being obtained, a venous cannula was inserted into a forearm vein, and either normal saline (following each of the first two treatment arms) or hydrocortisone 200 mg (following the third treatment arm, formoterol 12 µg b.i.d.) was given single-blind (patient) intravenously. The administration of steroid 1 h before measuring the dose-response to salbutamol was to mimic what might occur during an acute episode of asthma. Active hydrocortisone was given during the last of the three treatment periods to avoid any steroid-related carry over effect on β-adrenoceptor function.

Exactly 1 h later, patients underwent a methacholine challenge followed by a bronchodilator response measurement. The methacholine challenge was performed using a modified version of the rapid challenge procedure [28]. After measurement of baseline FEV1 according to American Thoracic Society (ATS) criteria [29] using a rolling seal spirometer (Spirotech, Graseby, Georgia, USA), increasing doses (0.044–45 µmol) of methacholine were administered by nebuliser, controlled by a Morgan Nebicheck dosimeter (Morgan, Gillingham, Kent, UK). The procedure was stopped after the FEV1 had fallen by ≥20%. The PD20 was calculated by linear interpolation.

Immediately after the PD20 had been reached, an abbreviated dose-response test to inhaled salbutamol (Ventolin, GlaxoWellcome, Greenford, UK) was undertaken. The salbutamol was administered from a metered dose inhaler via a large volume spacer (Volumatic, GlaxoWellcome, Greenford, UK). Doses of 100 µg, 100 µg, and 200 µg were given at 0, 5, and 10 min, respectively. Spirometry was performed immediately prior to each dose, and also at 15, 30 and 45 min.

A further 400 µg of salbutamol was administered at 45 min to maximise bronchodilatation prior to further spirometry and a second methacholine challenge at 60 min, using the same method as previously. The aim of this further challenge was to measure the protective effect of the salbutamol against further methacholine. Once a PD20 had been established for the second methacholine challenge, patients were given inhaled salbutamol ad lib and remained in the research laboratory until their FEV1 had returned to at least 90% of baseline.

**Analysis of results**

The primary study end-point was area under the curve (AUC) for change in FEV1 following inhaled salbutamol. From a previous investigation [27], the sample size was calculated so that there was 90% power to detect a 30% difference in AUC with a significance of 0.05. Analyses were undertaken to assess treatment-related differences, as well as the effects of intravenous hydrocortisone. Analyses of covariance were performed to take into account any differences in the baseline FEV1, the fall in FEV1 during the methacholine challenge and log PD20 methacholine. Where PD20 was not achieved after the highest dose of methacholine, an arbitrary value of 64 µmol was assigned. The increase in FEV1 after each dose of salbutamol, expressed as a percentage of the fall from baseline during the methacholine challenge, was also analysed.
Further comparisons were made for post-salbutamol PD20 values to assess treatment-related differences in the protective effect given by inhaled salbutamol against methacholine-induced bronchoconstriction. When comparing differences in the post-salbutamol PD20s between the first two treatment arms, the pre-salbutamol PD20 was used as a covariate.

Ethical considerations

Asthma control was carefully monitored throughout the study. Each patient had an individualised asthma action plan, a supply of prednisone and an inhaled β2-agonist for emergency use, and 24 h access to one of the study investigators, in case of an acute exacerbation. The study was approved by the Otago Ethics Committee. Each patient gave written informed consent.

Results

Twelve patients were enrolled into the study. Two patients withdrew following the run-in; one was unable to tolerate ipratropium as relief medication, the other developed diabetes mellitus. The ten randomised patients (9 female, aged 18 – 65 years) had a mean (95% confidence interval (CI)) FEV1 % predicted of 95.1% (82.9 – 107.3) on entry into the study. Their median (range) dose of inhaled corticosteroid was 800 mg.day⁻¹ (200 – 2000 mg) of beclomethasone or equivalent. One patient withdrew between the second and third treatment periods due to unstable asthma. Thus nine patients completed all three treatment arms of the study. Compliance with study medication was greater than 90% during each of the treatment arms.

Baseline lung function and bronchial hyper-responsiveness

Baseline FEV1 and mean methacholine PD20 values were not significantly different following each of the three treatment periods. The mean percentage fall in FEV1 did not differ between the treatments (table 1).

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Formoterol</th>
<th>Formoterol plus hydrocortisone</th>
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</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Baseline FEV1 L</td>
<td>2.59 (2.16 – 3.02)</td>
<td>2.59 (2.14 – 3.04)</td>
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<tr>
<td>PD20 for first methacholine challenge μmol</td>
<td>2.12 (0.57 – 3.67)</td>
<td>1.57 (0.34 – 2.80)</td>
</tr>
<tr>
<td>FEV1% fall from baseline %</td>
<td>25.91 (22.44 – 29.38)</td>
<td>25.81 (21.99 – 29.63)</td>
</tr>
<tr>
<td>AUC0–15</td>
<td>7.72 (6.84 – 8.60)</td>
<td>5.49 (4.61 – 6.37)</td>
</tr>
<tr>
<td>AUC0–45</td>
<td>35.36 (30.03 – 40.68)</td>
<td>24.94 (19.62 – 30.26)</td>
</tr>
<tr>
<td>FEV1 before second methacholine challenge</td>
<td>2.97 (2.81 – 3.13)</td>
<td>2.84 (2.68 – 3.00)</td>
</tr>
</tbody>
</table>

Results reported as mean (95% confidence interval). PD20: Provocative dose causing a ≥20% fall in forced expired volume in one second (FEV1).
measured by the increase in methacholine PD20 from baseline and expressed as doubling dose concentrations (d.d.s) was 2.74 d.d.s (95% C.I. 2.19 – 3.29) following formoterol and 3.97 d.d.s (95% C.I. 3.42 – 4.52) following placebo (p < 0.01). Following formoterol with hydrocortisone the increase in PD20 was 2.62 d.d.s (95% C.I. 2.01 – 3.23) (p = 0.79 for comparison with formoterol alone).

Discussion

The results of the present study show that in patients with mild to moderate asthma requiring maintenance inhaled steroid therapy, tolerance to the bronchodilator effect of salbutamol may be demonstrated in the presence of acute bronchoconstriction (mean fall in FEV1 26%) following treatment with regular formoterol. After salbutamol administration, the mean FEV1 was significantly lower at all time points and the AUC0–15 for change in FEV1 was reduced by 28.8% with regular formoterol compared to placebo. The magnitude of these changes is similar to what has previously been reported in a study using regular terbutaline [27]. In that investigation the AUC0–15 for FEV1 was reduced by 36.0%. Thus the present results confirm that bronchodilator tolerance develops during regular β-agonist treatment irrespective of whether a long or short-acting agent is being used.

The findings provide evidence that the effects of bronchodilator tolerance are more likely to be encountered when patients are experiencing bronchospasm. Most recent studies have failed to demonstrate bronchodilator tolerance with long-acting β-agonists [20–24]. This may be because these investigations have included patients whose asthma is stable and in whom there was no significant bronchoconstriction. For this reason, the validity of these earlier results is questionable. It is difficult to appropriately conduct controlled bronchodilator response studies in patients with unstable asthma. It was in an attempt to address this issue that mild airway obstruction was induced in the patients using a nonspecific bronchoconstrictor. Although the present model does not accurately mimic acute severe asthma, in which other factors besides β-adrenoceptor down-regulation, induced by continuous β-agonist therapy, may impair the response to inhaled bronchodilator, it does permit the conclusion that bronchodilator tolerance is more likely to be important in the presence of bronchoconstriction.

The study design included a 36 h period of drug withdrawal prior to testing for bronchodilator tolerance. If anything, this may have resulted in a diminution in the magnitude of the effect that was found, given that the status of β-adrenoceptors may change rapidly [30]. It might also be argued that testing for bronchodilator tolerance without a period of drug withdrawal would have been more clinically relevant. The principal reason for not doing so was to avoid the problem of functional antagonism to methacholine which would have resulted from the continuing action of formoterol. This would have had the potential to make acute bronchoconstriction, upon which demonstrating the development of tolerance was dependent, more difficult to achieve.

At 45 min our patients received a further 400 μg of salbutamol (making a total of 8 x 100 μg puffs) in order to induce maximal bronchodilatation. Following this, a significantly greater increase in FEV1 was achieved following formoterol treatment when compared to placebo (139 and 58 mL, respectively, p < 0.02). This indicates that at that time point, even though baseline FEV1 had been recovered, residual bronchoconstriction was still present following formoterol treatment, despite the fact that the patients had already received 400 μg (4 puffs) of salbutamol. Thus, as might have been anticipated, overcoming the effects of β-adrenoceptor tolerance required the use of higher doses of salbutamol, although there is evidence that this may not always be successful [31]. This suggests that, in circumstances of acute bronchoconstriction, patients taking long-acting β-agonists may require higher doses of "releiver" short-acting β-agonist in order to obtain maximum bronchodilatation.

The clinical importance of this is unclear. No studies have been carried out to examine the exact relationship between β-adrenoceptor tolerance and asthma control during long-term treatment with β-agonists. Nor is it known whether individual susceptibility to the development of tolerance influences how patients respond to treatment during acute life-threatening episodes. However, the results of other studies offer indirect but reassuring evidence. The frequency of asthma exacerbations is reduced with regular long-acting β-agonist, not increased [8, 9]. Furthermore, in a controlled study, changes in symptoms and peak flow rates during the early phases of an exacerbation do not appear to be different in patients receiving regular formoterol from those who are not [32]. In addition, the bronchodilator response to very high doses of nebulised salbutamol, such as would be used to treat acute severe asthma in an emergency department, is no different between patients taking or not taking regular salmeterol [33].

In the present study, prior administration of intravenous hydrocortisone 1 h before inducing
bronchoconstriction and giving salbutamol had no significant effect on the magnitude of bronchodilator tolerance. Even when an additional 400 μg of salbutamol was administered at 45 min i.e. 1 h and 45 min after giving hydrocortisone, the corticosteroid had no effect on the magnitude of the increase in FEV1 during the subsequent 15 min. This outcome is in apparent contrast to the report by Tan et al. [18], in which the combined use of both oral prednisone and intravenous hydrocortisone reversed bronchodilator tolerance to formoterol. However, in the present study patients were followed for only 2 h after giving corticosteroid, whereas Tan et al. [18] followed their patients for 8 h. Taken together, these results confirm that although giving corticosteroid is likely to be effective in reversing the effects of β2-adrenoceptor tolerance, it cannot be relied upon to do so in the early phases of an acute episode of asthma.

In conclusion, this study has demonstrated that significant tolerance to the bronchodilator effects of inhaled salbutamol occurs 36 h after cessation of formoterol. This effect is likely to be more important in circumstances of acute bronchoconstriction. Whether or not this effect increases with increasingly severe airway obstruction, or is accentuated when patients take excessive amounts of β2-agonist, requires to be evaluated further.

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References