Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled β-agonist treatment


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There is uncertainty about the development of airway tolerance to β-agonists and the phenomenon of rebound bronchoconstriction on β-agonist withdrawal. We have recently completed a study of the regular terbutaline and budesonide treatment in asthma. We report our observations on the effect of starting and stopping terbutaline treatment on morning and evening peak flows.

The study was a randomized four-way, double-dummy, cross-over comparison of regular inhaled terbutaline (500–1000 μg four times daily), budesonide, combined treatment and matching placebo. Each treatment was given for 6 weeks following a 4 week single-blind placebo washout. Ipratropium was used for symptom relief. No other asthma medication was permitted during either the treatment or wash-out periods. Evaluable data were obtained from 52 subjects for both placebo and terbutaline treatment. Changes in mean morning and evening peak flows during terbutaline treatment were compared to the baseline peak flows during the last 2 weeks of the preceding washout. The peak flow changes on stopping terbutaline were also analysed.

Mean morning peak flow was not significantly different during terbutaline treatment when compared to either baseline or placebo treatment. Evening peak flows were significantly higher during terbutaline treatment [mean increase 23.1 ± 1 l min⁻¹ (95% CI = 18.8, 27.4)]. Analysis of the peak flow changes on a day-by-day basis revealed an initial increase in morning peak flows for the first 2 days of treatment of 19.2 ± 2 l min⁻¹ [increases of 25.0 and 17.3 l min⁻¹ in comparison with the corresponding values during placebo (P < 0.01)] followed by a return to baseline. The increase in evening peak flows was also greater for the first 2 days of treatment than for the remainder of the treatment period (P < 0.01). On ceasing terbutaline treatment there was a fall in mean morning peak flow below the baseline on the following morning of 21.6 ± 1 l min⁻¹ (P < 0.05 compared to placebo).

The temporary increase in morning peak flows and greater than expected rise in evening peak flows for the first 2 days of treatment suggest the development of tolerance to the bronchodilator effect of terbutaline. Similarly, the fall in morning peak flows on treatment withdrawal suggests rebound bronchoconstriction. These effects are likely to be mediated by downregulation of the β-receptor during treatment. The clinical significance of these changes is uncertain in view of the stability of overall asthma control during terbutaline treatment, but sudden withdrawal of β-agonist treatment could conceivably lead to a deterioration in asthma control.

Key words: tolerance, β-agonists; asthma; adverse effects.
Downregulation of airway $\beta_2$-receptors may also explain the phenomenon of rebound bronchoconstriction on treatment withdrawal (8–10). Whether this withdrawal effect has clinical significance is unclear, but in some circumstances it could conceivably contribute to an acute deterioration in asthma control in patients with brittle asthma.

We have recently reported a study of terbutaline and budesonide treatment designed to examine the interaction between these drugs (11). The data obtained also allowed us to analyse the effects of starting and stopping terbutaline treatment. Our observations are reported here.

**Methods**

The study design has been reported elsewhere (11). In brief, volunteers aged 9–64 with mild to moderate atopic asthma and bronchial hyperresponsiveness to methacholine (PC$_{20}$≤8 mg ml$^{-1}$) were recruited. Subjects on high dose inhaled corticosteroids (>1500 $\mu$g day$^{-1}$ in adults, >800 $\mu$g day$^{-1}$ in children aged <13 years of age), oral steroids and current or ex-cigarette smokers (>5 pack years) were excluded. The study was approved by the Otago Ethics Committee. Each subject (or their parent/guardian) gave written informed consent.

The study was a double-blind, random-order, double-dummy, cross-over comparison of four treatments: terbutaline 1000 $\mu$g four times daily, budesonide 400 $\mu$g twice daily, both drugs and placebo. Doses were halved for children under 13 years. Each treatment was given for 6 weeks. Inhaled corticosteroid treatment was withdrawn for at least 2 weeks before starting a 4 week single-blind placebo run-in during which no asthma treatment was used other than inhaled ipratropium bromide as required for symptom relief. Identical 4-week single blind washouts were used between each treatment. Subjects continued to use inhaled ipratropium bromide for symptom relief throughout the study. No other asthma treatment was permitted except in the event of an exacerbation in which case the subject was withdrawn from the treatment period. Subjects kept a record of peak flows measured before the morning and evening doses of study inhalers. Spirometry and methacholine challenge tests were performed at the beginning and end of each treatment.

This analysis was a *post hoc* study of changes in morning and evening peak flow during terbutaline treatment. The mean changes in morning and evening peak flows were calculated for each day and each week of the treatment periods and washout intervals. The mean peak flows for the 2 weeks immediately prior to starting treatment, during which subjects were receiving single-blind placebo treatment, were used as the baseline for evaluating subsequent changes. Where data were available, the changes in peak flows on stopping treatment were also calculated. Unfortunately washout data were not collected following the last of the four treatment periods, hence these data are only available for approximately 75% of subjects. Changes from baseline on starting and stopping terbutaline were compared to the equivalent days on placebo using a one-way analysis of variance.

**Results**

Fifty-five subjects received terbutaline and 54 received placebo. One subject withdrew during terbutaline treatment because of tremor and had insufficient data for analysis. Two subjects were excluded from analysis because of irregularities with their peak flow recording. Thus data were analysed for 52 subjects taking each treatment. The mean values for lung function data obtained during each treatment period are shown in the Table 1.

Over the 6 weeks of regular treatment terbutaline did not significantly alter mean morning peak flow with respect to either baseline or placebo [mean (95% CI) increase from baseline 2.5 (-1.8, 6.8) l min$^{-1}$]. However, analysis of the daily peak flow changes showed a mean (95% CI) increase

*Change from baseline (mean peak flows during last 2 weeks of each run-in period); †Change from the value measured immediately before starting placebo or terbutaline treatment; ‡$\Delta$PD$_{20}$ is expressed as doubling dose changes. CI: confidence interval; FEV$_1$: Forced expiratory volume in 1 sec; FVC: Forced vital capacity, PD$_{20}$: provocational dose causing a 20% fall in FEV$_1$. 

<table>
<thead>
<tr>
<th></th>
<th>Placebo (95% CI)</th>
<th>Terbutaline (95% CI)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning peak flow</td>
<td>415 (390, 440)</td>
<td>417 (392, 442)</td>
<td>0.53</td>
</tr>
<tr>
<td>$\Delta$ Morning peak flow*</td>
<td>0.7 (−3.6, 5.0)</td>
<td>2.5 (−1.8, 6.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>Evening peak flow</td>
<td>423 (399, 447)</td>
<td>447 (423, 470)</td>
<td>0.0001</td>
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<tr>
<td>$\Delta$ Evening peak flow*</td>
<td>−0.7 (−4.8, 3.4)</td>
<td>23.1 (18.8, 27.4)</td>
<td>0.0001</td>
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<tr>
<td>FEV$_1$</td>
<td>2.91 (2.83, 2.99)</td>
<td>2.90 (2.81, 2.99)</td>
<td>0.87</td>
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<tr>
<td>$\Delta$ FEV$_1$†</td>
<td>−0.067 (−0.14, 0.01)</td>
<td>−0.083 (−0.17, 0)</td>
<td>0.78</td>
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<tr>
<td>FVC</td>
<td>3.76 (3.66, 3.85)</td>
<td>3.74 (3.64, 3.84)</td>
<td>0.81</td>
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<tr>
<td>$\Delta$ FVC†</td>
<td>−0.061 (−0.15, 0.03)</td>
<td>−0.094 (−0.19, 0)</td>
<td>0.64</td>
</tr>
<tr>
<td>Geometric mean PD$_{20}$</td>
<td>0.524 (0.40, 0.68)</td>
<td>0.637 (0.48, 0.85)</td>
<td>0.38</td>
</tr>
<tr>
<td>$\Delta$ PD$_{20}$ change†</td>
<td>0.024 (−0.31, 0.35)</td>
<td>0.094 (−0.29, 0.47)</td>
<td>0.84</td>
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of 19·2 (7·8, 30·6) and 13·4 (2·1, 24·7) l min\(^{-1}\) above baseline for the first two mornings of terbutaline treatment followed by a return to baseline by day 3 (Fig. 1). When compared to the corresponding days during placebo the mean peak flows were 25·0 and 17·3 l min\(^{-1}\) higher during terbutaline \((P<0.002\) and \(P<0.01\), respectively).

On withdrawal of terbutaline there was a fall of 21·6 (4·1, 39·1) l min\(^{-1}\) below baseline on the first morning after stopping treatment. This was significantly lower than placebo [mean difference between terbutaline and placebo of 23·1 l min\(^{-1}\) \((P=0.024)\)]. Peak flows on the second morning after stopping terbutaline were not significantly different from placebo and returned to baseline by day 3 (Fig. 1).

Evening peak flows were significantly higher during terbutaline treatment than during the baseline or placebo. The mean (95% CI) increase from baseline was 23·1 (18·8, 27·4) l min\(^{-1}\) \((P<0.001)\). The increases in evening peak flows on the first and second days of terbutaline treatment were significantly greater than this mean change [mean (95% CI) increase 32·7 (19·5, 45·9) and 35·4 (24·1, 46·7) l min\(^{-1}\) respectively; \(P=0.014\) and \(P<0.0002\)] (Fig. 2).

After terbutaline was discontinued there was a small fall in evening peak flows below baseline [mean (95% CI) 8·31 l min\(^{-1}\)]. This was not significantly lower than the baseline but was of borderline significance compared to placebo (mean difference between placebo and terbutaline of 22·5 l min\(^{-1}\), \(P=0.055\)) (Fig. 1).

**Discussion**

The observations reported here were not based on an *a priori* hypothesis and require cautious interpretation. However, they strongly suggest the development of tolerance to the bronchodilator effect of terbutaline occurring within 2 days of starting treatment and that rebound bronchoconstriction occurred for a similar interval when terbutaline was withdrawn.

The increase in morning peak flows observed on starting terbutaline treatment was unexpected since morning peak flows were measured before the first daily dose of terbutaline. However, this would be consistent with the evening doses having had a prolonged bronchodilator effect for the first 2 days of treatment, followed by the development of tachyphylaxis to its duration of action by the third day. Shortening of the duration of the bronchodilator action of \(\beta\)-agonists has been described previously, although the time course for this effect has not (12–15).

![Fig. 1. Time trends in (a) morning and (b) evening peak flows before, during and after terbutaline treatment. Mean (+95% CI) changes from baseline are shown for each day of the weeks before (run-in) and after starting terbutaline, for the 6 weeks of the treatment period, and for each day of the weeks before and after stopping treatment. Mean changes of the placebo treatment period are indicated by the broken line. The baseline was defined as the mean peak flow of the last 2 weeks of each of the pre-treatment washouts.](image-url)
Evening peak flows were measured before the final daily dose of study medication — typically 4–5h after the afternoon dose. The finding that the increase in mean peak flow was greater for the first two evenings of terbutaline than during the remainder of the treatment period suggests that this may also have been affected by tachyphylaxis. A similar effect was noted in a study of the long-acting β₂-agonist, formoterol, in which there was a reduced increase in peak flows after 2 days of treatment (16). However, in that study, the use of a long-acting β₂-agonist meant that this effect was observed in morning peak flows which were measured after a longer (overnight) interval after administration of the previous dose.

The fall in mean peak flow below baseline on the first morning after stopping terbutaline treatment suggests rebound bronchoconstriction. This is consistent with previous findings (8–10). The effect was not caused by the methacholine challenge procedure at the clinic visit since it was not observed at the time of stopping placebo treatment. However, the use of salbutamol after the methacholine challenge may have masked a rebound fall in evening peak flow on the day of terbutaline withdrawal. Thus the mean evening peak flow did not fall significantly below baseline on this day, but did appear to be reduced compared to placebo ($P=0.055$).

The timing of these changes is consistent with evidence that downregulation of β₂-receptors on bronchial epithelial cells and alveolar macrophages occurs after 24h of regular inhaled β₂-agonist treatment (17). Our data suggest that spontaneous recovery of β₂-receptor function in bronchial smooth muscle occurs over a similar period.

The effects of regular terbutaline on overall asthma control, spirometry, bronchial hyperresponsiveness to methacholine and morning peak flows in this study have previously been reported (11). There was no evidence that terbutaline had an adverse effect on any of these outcomes over the 6 week study period (Table 1). However, the observations reported here suggest that terbutaline treatment leads to significant downregulation of airway β₂-receptors. The clinical significance is uncertain in view of the overall stability of asthma control during terbutaline. The magnitude of the mean peak flow changes reported here is not large (approximately 201 min⁻¹) and recovery of β-receptor function appears to be rapid. Despite this it is possible that loss of β-receptor function during regular β₂-agonist treatment contributes to an acute deterioration in asthma control if treatment is stopped abruptly in some patients. We have demonstrated that patients may fail to respond adequately to bronchodilator as a result of regular β₂-agonist use (17). A combination of these factors may partly explain the association between frequent use of β₂-agonists with asthma mortality (18,19).

Acknowledgements

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References


