Tolerance to beta-agonists during acute bronchoconstriction

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ABSTRACT: Previous reports suggest that regular use of β-agonists does not lead to tolerance to their bronchodilator effects. However, most studies have been conducted in stable asthma. This study investigates whether bronchodilator tolerance can be demonstrated during acute bronchoconstriction.

Thirty-four asthmatic subjects were treated with 6 weeks inhaled terbutaline (1 mg *q.i.d.*), budesonide (400 μg, *b.i.d.*), both drugs or placebo in a randomized, double-blind, cross-over study. After each treatment methacholine was administered to induce a 20% fall in the forced expiratory volume in one second (FEV_1). The response to inhaled salbutamol 100, 100, 200 μg at 5 min intervals) was then measured. Dose-response curves were compared using an analysis of covariance. Pre-methacholine FEV_1, the highest pre-methacholine FEV_1, the fall in FEV_1 induced by methacholine and the logarithm of the provocative dose of methacholine required to induce the 20% fall in FEV_1 (PD_{20}) were used as covariates.

There was a significantly reduced response to salbutamol after 6 weeks terbutaline treatment: the mean (95% confidence intervals (CI)) area under the dose-response curve was reduced by 36% (24, 47) compared to placebo ($p<0.0001$). The reduction in bronchodilator response was not affected by concomitant treatment with budesonide.

Significant tolerance to the bronchodilator effect of inhaled β-agonists may be demonstrated when tested during acute bronchoconstriction. Continuous treatment with inhaled β-agonists may lead to a reduced response to emergency β-agonist treatment during asthma exacerbations.
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β-agonists are highly effective bronchodilators and have an important role in the treatment of asthma exacerbations. However, many of the pharmacological effects of β-agonists diminish during chronic treatment, and there has been some concern that regular use of these drugs could lead to a failure to respond to treatment during severe asthma attacks. Some recent studies have shown a small reduction in bronchodilator response during treatment with long-acting β-agonists [1–3], but in general asthmatics have been found to be surprisingly resistant to the development of bronchodilator tolerance [4, 5]. The reason for this is unknown. It may be because there is a high turnover of β_2-receptors on airway smooth muscle such that receptor down-regulation has little impact on the receptor density [6]. Alternatively, it may be because maximal bronchodilation can be achieved by stimulation of a fraction of the normal receptor number.

In contrast, there is increasing evidence that continuous β-agonist treatment leads to a reduction in their bronchoprotective effect for a variety of bronchoconstricting stimuli including methacholine, histamine, adenosine, exercise and allergen [7]. However, the clinical significance of these changes is uncertain in view of the apparently preserved acute bronchodilator response.

This dissociation between the tendency to develop tolerance to the bronchodilator and bronchoprotective effects has not been adequately explained. It has been suggested that the two effects have distinct mechanisms. The bronchoprotective effect may involve β_2-receptors other than those on airway smooth muscle, such as those on airway mast cells which have a greater propensity to down-regulation [8–10]. Alternatively, it is possible that both effects are mediated by receptors on airway smooth muscle, but that a greater degree of receptor activation is required to maintain bronchodilation in the presence of a constricting stimulus. If this is the case, then although tolerance to the bronchodilator effect of β-agonists is difficult to demonstrate during stable asthma, it may be a significant problem during acute severe asthma because of the influence of bronchoconstricting mediators.

As part of a study of the effects of terbutaline and budesonide on inflammatory markers in induced sputum (unpublished data) the authors took the opportunity to study the effect of 6 weeks treatment with these drugs on the response to inhaled salbutamol. It was hypothesized that tolerance to the bronchodilator effect could be demonstrated if tested in the presence of a bronchoconstricting stimulus. In order to assess this, dose-response curves to salbutamol were constructed after methacholine challenge.

Methods

Subjects

Volunteers aged 16–64 yrs with mild to moderate atopic asthma were recruited in two centres (Dunedin and Christchurch, New Zealand). All had bronchial hyperresponsiveness to methacholine (provocative concentration causing a 20% fall in forced expiratory volume in one second (FEV1) (PC20) <8 mg·mL^{-1} [11] or provocative dose causing a 20% fall in FEV1 (PD20) <8 μmol [12]). Subjects using high dose inhaled corticosteroids (>1500 μg·day^{-1}) or maintenance oral corticosteroids were excluded for safety reasons. Current or previously heavy cigarette smokers (>5 pack-yrs) were also excluded.

Study design

Each subject entered a 4-week run-in during which all asthma treatment other than as required bronchodilators was discontinued. Subjects who were unable to tolerate the withdrawal of maintenance treatment and those who did not have bronchial hyperresponsiveness to methacholine at the end of the run-in (PD20 <8 μmol) were withdrawn. The remaining subjects were randomized to a double-blind sequence of four treatments. The treatments were terbutaline (Astra Draco, Lund, Sweden) 1000 μg q.i.d., budesonide (Astra Draco) 400 μg b.i.d., both drugs (combined treatment) and placebo. The drugs were administered by dry powder inhaler (Turbuhaler; Astra Draco). Dummy inhalers were used to maintain blinding. Each treatment was given for ≥6 weeks. Subjects used ipratropium bromide 40 μg·puff^{-1} (Boehringer Ingelheim, Ingelheim Germany) for symptom relief during the treatment periods. No other asthma treatment was permitted except in the event of an exacerbation.

Subjects experiencing an exacerbation of their asthma requiring additional medication during any one of the treatment periods were withdrawn from that treatment period and treated appropriately. The treatment period was not repeated. However the subjects were eligible to complete the remaining treatment periods providing asthma stability had been re-established.

Measurements

Methacholine challenges and bronchodilator response tests were performed at the end of each treatment period. Study medications and ipratropium were withheld for ≥6 h before the procedure. The methacholine challenge was performed using a modified version of the rapid challenge procedure [12]: after measurement of baseline FEV1, increasing doses (0.044–45 μmol) of methacholine were administered by nebulizer controlled by a Nebicheck Ædosimeter (Morgan, Gillingham, Kent, UK). The procedure was stopped after the FEV1 had fallen by ≥20%. The PD20 was calculated by linear interpolation.

Immediately after a 20% fall in FEV1 had been achieved an abbreviated dose-response test to salbutamol (Glaxo-Wellcome, Greenford, UK) was commenced. Three doses (100, 100, and 200 μg) of salbutamol were administered from a metered dose inhaler via a large volume spacer (Volumatic; GlaxoWellcome) at 5 min intervals. The FEV1 was measured 5 min after each dose.

The dose-response test was terminated after 15 min because it was anticipated that spontaneous recovery from the methacholine challenge would confound the results if further doses or longer intervals between doses were used. The spontaneous improvement in FEV1 following methacholine challenge was measured in an open study by constructing dose-response curves to placebo salbutamol using an identical protocol in 10 of the subjects after they had completed the main study.

Analysis of results

An analysis of covariance ("mixed procedure", ìProc. Mix; SAS institute, Cary, NC, USA) was performed to take into account treatment-related differences in the baseline (premethacholine) FEV1, the fall in FEV1 during the methacholine challenge (FEV1, fall), the highest of the four baseline FEV1 values (taken to represent near-maximal bronchodilation for that individual) and log PD20 methacholine. Where a 20% fall in FEV1 was not achieved after the highest dose of methacholine an arbitrary value of 64 μmol was assigned. Dose-response curves were analysed as the mean area under the curve (AUC). 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.

Ethical considerations

Asthma control was carefully monitored throughout the study. Each subject had an asthma action plan, a supply of prednisone, a β2-agonist inhaler and 24 h access to one of the investigators in case of an exacerbation. The study was approved by the Southern Regional Health Authority (Otago and Canterbury, New Zealand) Ethics Committees. Each subject gave written informed consent to the study.

Results

Of 52 subjects recruited to the study, 34 (18 male, aged 17–61 yrs) were randomized to the treatment periods. These subjects had a mean (95% confidence intervals (CI)) per cent predicted FEV1 of 89.5% (85.3, 93.7) on recruitment to the study. Six subjects failed to complete the study (four because of poor asthma control, two withdrew consent). No dose-response data were obtained for five of these. Dose-response curves for at least one treatment period were obtained on 29 subjects. No dose-response data were obtained in 10 treatment periods (five terbutaline, four placebo, one combined) which were curtailed because of exacerbations of asthma requiring additional treatment. An analysis which included only the 22 subjects who completed all four treatment periods provided similar results to those presented below.

Baseline lung function and bronchial hyperresponsiveness

Baseline FEV1 and geometric mean PD20 values were higher after budesonide and combined treatment than after terbutaline or placebo treatment (p<0.002 for FEV1, p<0.0001 for PD20) (table 1). There were no significant differences between budesonide and combined treatment or between terbutaline and placebo.

Table 1. – Baseline lung function, bronchial hyperresponsiveness and dose response to salbutamol after each treatment period

	Placebo	Budesonide	Terbutaline	Combined
Subjects n	25	28	24	28
Baseline FEV1 (95% CI)	2.97 (2.68, 3.26)	3.18 (2.89, 3.47)	2.83 (2.54, 3.12)	3.16 (2.87, 3.45)
PD20 (95% CI) µmol	0.68 (0.40, 1.16)	2.48 (1.48, 4.15)	0.54 (0.31, 0.92)	2.40 (1.43, 4.03)
FEV1 (95%CI) % fall	28.4 (24.9, 31.6)	26.1 (22.3, 28.3)	26.9 (24.4, 28.5)	25.9 (22.2, 28.2)
Area under curve*	297 (261, 333)	275 (239, 310)	191 (151, 231)	184 (148, 219)
80% recovery n% ‡	20 (80)	23 (82)	10 (42)	10 (36)

*: model estimates from analysis of covariance; ‡: recovery of 80% of the difference between the post-methacholine forced expiratory volume in one second (FEV1) and the highest baseline FEV1. 95% CI: 95% confidence intervals; PD20: provocative dose of methacholine causing a 20% decrease in FEV1.

Dose-response curves to salbutamol

The dose-response curves are shown in fig. 1. The mean percentage fall in FEV1 during the methacholine challenges did not differ between the treatments (table 1). However. because the baseline FEV1 values were lower after terbutaline and placebo treatment than after budesonide or combined treatment (fig. 1), the mean FEV1 values following the methacholine challenges were also correspondingly lower.
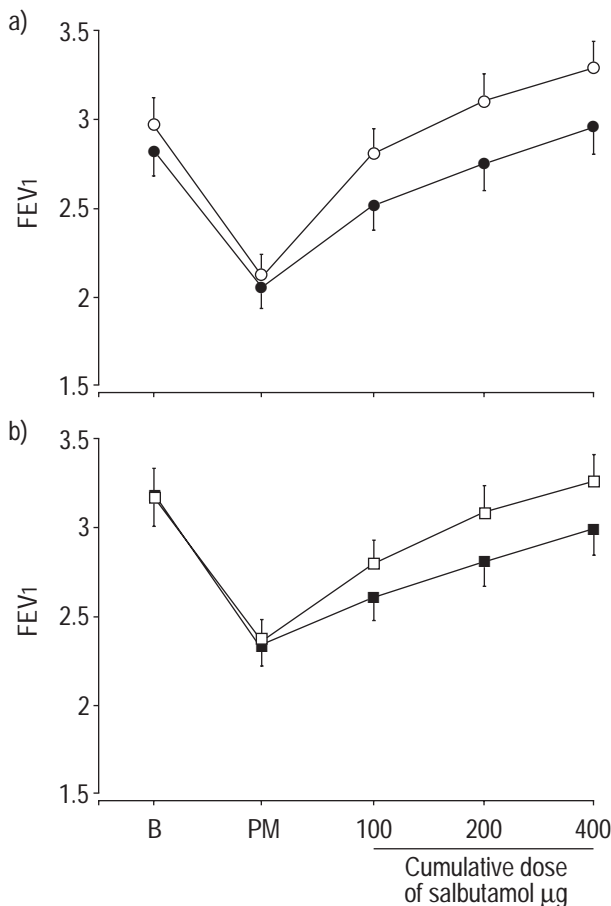
The baseline FEV1, the fall in FEV1 after methacholine, the maximum baseline FEV1 and log PD20 were all significant covariates for AUC (p<0.01). The mean (95% CI) AUC was 36% (24, 47) lower after terbutaline than after placebo, and 33% (22, 44) lower after combined treatment than after budesonide (both p<0.0001). The AUC did not differ between placebo and budesonide treatment or between terbutaline and combined treatment (table 1).

The improvements in FEV1 (as a per cent of the fall during the challenge) for each of the doses of salbutamol were greater after placebo than after terbutaline (p< 0.0001). Similarly, they were also greater after budesonide than after combined treatment (p<0.0005). There were no significant differences between the responses after budesonide and placebo, or between terbutaline and combined treatment (table 1, fig. 2).

The number of subjects recovering 80% of the methacholine-induced fall in FEV1 after the highest dose of salbutamol was reduced following terbutaline or combined treatment. When expressed as recovery of the difference between the post-methacholine FEV1 and the highest baseline FEV1, significantly fewer subjects achieved ≥80%

Fig. 1. – Dose response curves to salbutamol. Data are presented as mean±SEM. The baseline (B) forced expiratory volume in one second (FEV1) was measured immediately prior to the methacholine challenge for a) placebo or terbutaline treatment and b) budesonide or budesonide and terbutaline treatment. PM: post-methacholine; ○: placebo; ●: terbutaline; □: budesonide; ■: budesonide + terbutaline.
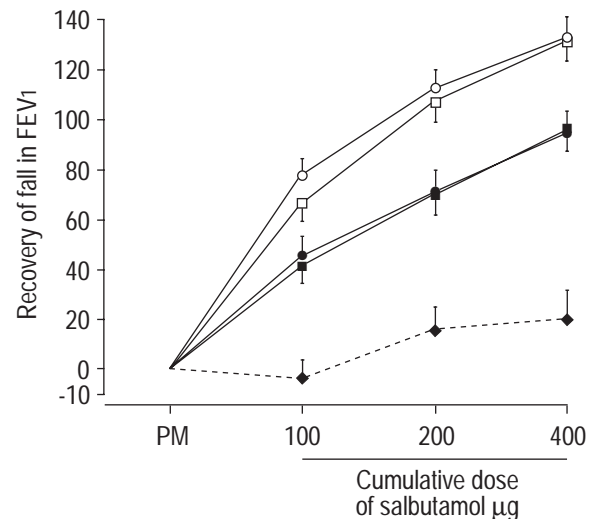

Fig. 2. – Per cent recovery of the forced expiratory volume in one second (FEV1) in response to salbutamol. Data are presented as mean± SEM. Values are model estimates from the analysis of covariance which adjusts for the effect of baseline FEV1, FEV1 fall, highest baseline FEV1 and log provocative dose causing a 20% fall in FEV1 (PD20). - - - - : recovery of FEV1 in response to placebo salbutamol in 10 of the subjects; ◆: placebo salbutamol; ■: budesonide + terbutaline; ●: terbutaline; □: budesonide; ○: placebo; PM: post-methacholine.

recovery after terbutaline than placebo (p<0.01) or after combined treatment than budesonide (p<0.001) (table 1).

The dose-response curves to placebo salbutamol (in 10 subjects) showed no significant change in FEV1, although there was a trend to recovery after 10 and 15 min. The mean (95% CI) recovery of FEV1 was -4%, (-20, 11), 15% (-2, 32), 19% (-3, 40) after, 5, 10 and 15 min respectively (fig. 2).

Discussion

This study has demonstrated that significant tolerance to the bronchodilator response to β-agonists occurs after regular treatment. Concomitant treatment with inhaled corticosteroid did not prevent the development of tolerance. These findings were not due to underlying changes in lung function or the degree of hyperresponsiveness. Baseline FEV1 and PD20 values did not differ significantly between placebo and terbutaline treatment, yet there was a highly significant difference in the dose-response curves to salbutamol after these treatments. Similarly the dose-response curves following budesonide and budesonide+terbutaline treatment differed despite almost identical baseline FEV1 and PD20 values.

These results contrast with those of most previous studies which have failed to demonstrate bronchodilator tolerance to short-acting β-agonists [4, 5]. The difference between this and previous studies is that this study tested the bronchodilator response after bronchoconstriction had been induced by methacholine. The results indicate that loss of β2-receptor responsiveness is easier to demonstrate under conditions of increased bronchomotor tone. A similar approach was used by LARSSON et al. [13] who tested the response to inhaled terbutaline following allergen challenge. In that study there was a reduced response to inhaled terbutaline as measured by peak flow and specific airway conductance after 2 weeks of treatment with oral terbutaline. However, following allergen challenge the response to β-agonists may include both smooth muscle relaxation and inhibition of further mediator release from inflammatory cells. The use of methacholine, a direct smooth muscle stimulant, in the present study makes it clear that tolerance occurs in airway smooth muscle.

The method used to demonstrate bronchodilator tolerance in this study is novel. A potential problem with this approach is that the bronchodilator response to salbutamol may be confounded by spontaneous recovery from the bronchoconstricting effects of methacholine. For this reason the dose-response measurements were concluded at 15 min. The response to placebo salbutamol in 10 of the study participants confirmed that little spontaneous recovery occurred during this time interval, and it is unlikely that this significantly affected the results.

The results lead the authors to question the distinction made between the bronchodilator and bronchoprotective effects of β-agonists. It has been suggested that these two effects may have different mechanisms because it has been easier to demonstrate tolerance to the nonbronchodilator effects [8]. However, measurement of bronchodilation is limited by return to "normal" [7]. In stable asthma this may be achieved by low levels of β2-receptor occupancy and the bronchodilator response may therefore be maintained despite receptor down-regulation. In contrast, in the presence of a constricting stimulus, maintenance of airway smooth muscle relaxation may require more β2-receptor activity, and tolerance is easier to demonstrate.

The results suggest that continuous treatment with a β-agonist could lead to a failure to respond to supplementary "reliever" β-agonist treatment during acute episodes of asthma. After inducing a 20–30% fall in FEV1 using methacholine a significant reduction in the bronchodilator response during regular β-agonist treatment could be demonstrated. Much greater reductions in lung function occur in acute severe asthma and the loss of the bronchodilator response is likely to be correspondingly greater. There have been anecdotal reports of a failure to respond to β-agonists during acute severe asthma [14, 15]. Although a failure to respond to bronchodilators might also be due to other factors such as airway mucus plugging and mucosal oedema, the results of the present study indicate that, at least in part, this may be due to prior use of β-agonists. They offer a possible explanation for the association between β-agonist use and asthma mortality [16]. Because of the time constraints, the maximum dose of salbutamol administered was 400 μg. It is possible that the high doses of nebulized β-agonist which are routinely used in emergency departments would overcome the effects of tolerance. However, most asthma exacerbations in the community are initially treated with β-agonists in doses similar to those employed in this study. Of importance is the observation that concomitant inhaled corticosteroid treatment did not prevent the development of tolerance. This was despite the fact that single doses of systemic corticosteroid have been shown to reverse β-receptor down-regulation [17], but is in keeping with earlier findings that inhaled corticosteroids do not prevent tolerance to the bronchoprotective effects of β-agonists [18–20].

These results provide further support for current guidelines [21] that short-acting β-agonists should be used only as required. Although the effects of long-acting β-agonists, which are intended for maintenance therapy, have not been studied using this model, it seems likely that similar outcomes would emerge. These agents lead to a greater loss of the bronchoprotective effect than short-acting drugs [7] and tolerance to the bronchodilator effect has been demonstrated even using conventional techniques [1–3]. The results of the present study raise the possibility that in the setting of a severe asthma attack, loss of the bronchodilator response as a result of treatment with a long-acting β-agonist may be important.

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