

Influence of budesonide on the response to inhaled terbutaline in children with mild asthma

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The aim of this study was to evaluate if continuous treatment with budesonide or salmeterol influences the bronchodilator response to terbutaline in children with asthma; 23 children, aged 7 to 16 years (mean = 11 years), with mild asthma were treated with inhaled budesonide 100 µg b.i.d. and placebo for three weeks in a randomized, double blind cross-over study. These treatments were followed by treatment with inhaled salmeterol 50 µg b.i.d. for 3 weeks. On the last day of each period a cumulative dose-response experiment with terbutaline in the doses 50, 100, 250 and 500 µg (cumulative dose 900 µg) was performed. Lung function was measured before and 20 min after each terbutaline inhalation. Baseline pulmonary functions after budesonide treatment were significantly higher than the baseline measured after the two other treatments ($p < 0.05$). After budesonide treatment, the dose-response curve was shifted vertically upwards but otherwise parallel to the dose-response curve after placebo. The increase from baseline after the first cumulative dose of terbutaline was significantly lower after salmeterol treatment than after the two other treatments ($p < 0.01$). Maximal lung functions after 900 µg terbutaline also differed significantly between the three dose-response days; budesonide being significantly higher and salmeterol significantly lower than placebo ($p = 0.02$ and $p < 0.001$, respectively). It is concluded that budesonide treatment does not enhance the bronchodilator response to terbutaline. Further studies are needed to assess if long-term continuous salmeterol treatment reduces the response to terbutaline.

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Treatment of asthma with inhaled β_2 agonists and the mechanism of β_2 receptor function have been subjects of concern during the recent years and the appropriateness of regular use of β_2 agonists is often discussed (1–5).

In an earlier study (6) we have found that the effect-drug concentration (E/C) curves after intravenous administration of terbutaline to children with asthma could be divided into two subgroups: those with a steep E/C curve and those with a flat E/C curve. Apart from compliance with the inhaled corticosteroid there was no obvious differences between the two groups. Our hypothesis was that administration of inhaled corticosteroid in addition to its antiinflammatory effects might enhance the response elicited from the inhaled β_2 agonist via a steroid effect on the β_2 receptor level (7).

The aim of the present study was to evaluate whether treatment with inhaled corticosteroid could

influence the shape of the dose-response curve after inhalation of cumulated doses of terbutaline. Furthermore, when the cross-over study was planned the long acting β_2 agonist salmeterol was introduced. We found it important also to study the effects of regular salmeterol administration because of the concerns raised about the appropriateness of regular use of β_2 agonists (1–4) and the discussions about where in the treatment plan to posit this drug: before or after the introduction of inhaled corticosteroids. Therefore, we decided, as an open study, to add an additional terbutaline dose-response experiment after a period with regular salmeterol treatment to compare this terbutaline dose-response curve with the dose-response curves after budesonide and placebo treatment.

Patients and methods

Children aged 7–16 years with mild asthma were included in the study. All had been taught in correct inhalation technique with the dry powder inhalers and the large volume spacer (Nebuhaler) which were used in the study. In addition all had been trained in correct peak flow monitoring on a Mini Wright peak flow meter and lung function measured on a Vitalograph. The patients were included in the study if their asthma was assessed as mild i.e. well controlled on a low dose of inhaled budesonide and if they for 2 weeks prior to the study were stable and well controlled on inhaled budesonide 200 µg b.i.d. from a pressurized metered dose aerosol (MDI) with a Nebuhaler or 100 µg budesonide b.i.d. from a Turbuhaler and inhaled β_2 agonist p.r.n. All had been on this treatment for at least 3 months prior to the study.

The study was planned as a randomized double-blind two-period cross-over study. At study entry, the patients were allocated to either inhaled placebo or inhaled budesonide (Spirocort Turbuhaler) 100 µg morning and evening. After three weeks, the patients switched over to the alternative regime without any washout. After these 2 treatment periods, all patients were treated openly with salmeterol (Serevent powder inhaler) 50 µg morning and evening for another three-week period. Inhaled terbutaline 0.5 mg (Turbuhaler) was allowed as p.r.n. medication. The need for this was recorded on diary cards. During the three treatment periods the patients also recorded peak expiratory flow rate (PEF), asthma symptoms and side-effects in the diary cards. Peak flow rate was measured before medication every morning and evening and the best of three measurements noted. Asthma symptoms were scored according to a rating scale. 0 = none, 1 = mild, 2 = moderate, and 3 = severe and general well being on a scale from 0–2. 0 = harmonious, happy extrovert, healthy and full of energy, 1 = quiet, low-spirited, a little tired, not so much energy, 2 = irritable, apt to cry, hyperactive.

At the end of each period a dose-response experiment was carried out to investigate the response to a β_2 agonist, terbutaline. Cumulative doses of 50, 100, 250 and 500 µg terbutaline from a MDI with a Nebuhaler were inhaled at 20 min intervals. The 50 µg terbutaline canisters were specially produced by Astra for the study. FEV₁ and FEF_{25–75} were asured on a Vitalograph before and 20 min after each treatment. The best of three measurements was recorded. The dose-response experiment always took place at the same time ($\pm$ one hour) in the morning. Systemic side effects were evaluated by measuring pulse rate and asking patients for side effects. Tremor was recorded by the investigator who subjectively as-

sessed the tremor of the fingers of the patient's extended hands. Tremor was graded on a scale from 0–3. On the dose-response study days the children were instructed to withhold treatment with budesonide and terbutaline or salmeterol for 14–17 h before the dose-response experiment with terbutaline.

Compliance with the treatment at home was assessed by counting the number of doses left in the turbuhaler after the treatment period and comparing this with the expected number if all doses had been taken. For salmeterol the number of empty blisters was counted when the child returned the inhaler and medication after treatment period.

In case of deterioration in PEF to a value < 70% of the child's personal best value the patients were instructed to contact the investigator to stop the treatment period. A terbutaline dose-response study was then performed and the patient went on to the next treatment period. The code remained unbroken. Compliance with the home treatment was assessed upon the recordings in the diaries. The number of doses derived from these recordings was calculated as % of the prescribed doses. Informed consent was given by the patients and their parents and the study was approved by the local ethics committee.

Statistical methods

Dose-response curves – Lung function pharmacodynamic parameters were compared between randomized treatments by assuming a multiplicative ANOVA model with factors patients, period and the treatment and then estimating the treatment effect. When the salmeterol treatment was compared with the other treatments a multiplicative ANOVA model with factors patients and treatment was used followed by pairwise comparisons between treatments. This analysis assumes that there was no period effect. Treatment differences were exponentiated to give a mean treatment in percent of mean treatment. Using a logarithmic model and exponentiating the means of the logarithmic data implies that we are working with geometric means. The mean value curves presented are those of adjusted mean values after exponentiation. They are referred to as adjusted geometric mean values.

The following pharmacodynamic definition of lung function parameters are used: Ebase = the basal value of a lung function test expressed as a percentage of the maximal value during all three dose-response trials.

E_{max} = the difference between the maximal value of a lung function test expressed as a percentage of the maximal value during all three dose-response trials.

Table 1. Pharmacodynamic parameters for FEV₁ (mean ± SD)

	Ebase	E _{max}	ΔE	ΔE 50 μg
Budesonide (A)	90.0 ± 4.8	98.9 ± 2.1	10.2 ± 6.1	0.116 ± 0.117
Placebo (B)	85.9 ± 8.5	96.5 ± 3.8	13.2 ± 10.2	0.139 ± 0.141
Salmeterol (C)	86.5 ± 11.7	93.4 ± 7.4	9.4 ± 13.8	0.038 ± 0.158
p value	A > B (p = 0.04) n.s. n.s.	A > B (p = 0.02) A > C (p < 0.01) B > C (p < 0.03)	n.s. n.s. n.s.	n.s. A > C (p = 0.02) B > C (p < 0.01)

ΔE = the difference between the maximal value and the basal value for a particular dose-response trial in percent of the same basal value.

ΔE 50 μg = the increase from baseline to first cumulative dose in a particular dose-response trial. This is considered a measure of the steepness of the dose-response curve and is measured in the units of the response variable.

For diary data the observations from Days 8 to 20 were analyzed in the same way as lung function data. For PEF the model was multiplicative but for the remaining variables the model was additive.

Results

Twenty-three patients completed all three periods. Twelve patients received placebo as first treatment and 11 received budesonide. In the third period all patients were treated with salmeterol. Compliance was high (>85% in all periods) in 19 patients, and no patient took less than 67% of the prescribed medication. Their mean age was 11.5 (range 7–16) years. Pharmacodynamic parameters for the 23 patients are given in Tables 1 and 2.

Double blind

Dose-response studies

FEV₁ – Mean baseline FEV₁ after placebo treatment varied from 67.8% to 97.3% and baseline FEV₁ was significantly higher after budesonide than after placebo treatment (Table 1, Fig. 1). The shape of the dose-response curves on the two days were similar and there was no statistically significant difference in ΔE and ΔE 50 μg between the dose-response experiment after placebo and budesonide. The curves were completely parallel with the curve after

budesonide treatment shifted vertically upwards so that E_{max} after budesonide treatment was also significantly higher than after placebo (p = 0.02).

FEF_{25–75} – As for FEV₁ baseline FEF_{25–75} and E_{max} after budesonide treatment were statistically significantly higher than baseline after placebo treatment (Table 1, Fig. 1). The percent increase from baseline versus a logarithmic dose-scale is shown in Fig. 2. The dose-response curves were identical and parallel and there was no statistically significant difference in ΔE or ΔE 50 μg between the two treatments.

Open

FEV₁ – Baseline FEV₁ after salmeterol varied from 62.8% to 100% and did not differ from baseline after placebo or budesonide (Table 1). However, E_{max} and ΔE 50 μg were significantly lower in the dose-response experiment after salmeterol than in the dose-response experiment after placebo or budesonide treatment. ΔE did not differ between the three treatments. It seemed as if salmeterol treatment caused a downward shift in the terbutaline dose-response curve (Fig. 1).

FEF_{25–75} – Baseline FEF_{25–75} after salmeterol was similar to placebo and significantly lower than baseline after budesonide treatment (Table 2) and salmeterol caused a downward shift in the terbutaline dose-response curve (Figs 1, 2). As for FEV₁ E_{max} and ΔE 50 μg were significantly lower in the dose-response experiment after salmeterol than in the dose-response experiments after the two treatments. In addition ΔE was significantly lower than ΔE after placebo.

Mean baseline pulse rate was the same for all treatments (budesonide = 73, placebo = 74, salmeterol = 74 beats per min) and there was no statistically significant difference between the three treatments in increase in pulse rate (budesonide = 7, placebo = 7, and salmeterol = 10 beats per min). Furthermore, there was no difference between the three treatments in occurrence of tremor (budesonide 7, placebo and salmeterol = 8 patients).

Table 2. Pharmacodynamic parameters for FEF_{25–75} (mean ± SD)

	Ebase	E _{max}	ΔE	ΔE 50 μg
Budesonide (A)	77.9 ± 9.8	99.2 ± 2.4	29.6 ± 19.1	0.243 ± 0.263
Placebo (B)	67.7 ± 13.8	92.6 ± 7.5	41.3 ± 25.9	0.300 ± 0.297
Salmeterol (C)	70.5 ± 17.1	83.1 ± 12.0	24.9 ± 36.2	0.048 ± 0.300
p value	A > B (p = 0.006) A > C (p < 0.02) n.s.	A > B (p = 0.002) A > C (p < 0.001) B > C (p < 0.001)	n.s. n.s. B > C (p < 0.005)	n.s. A > C (p = 0.01) B > C (p < 0.002)

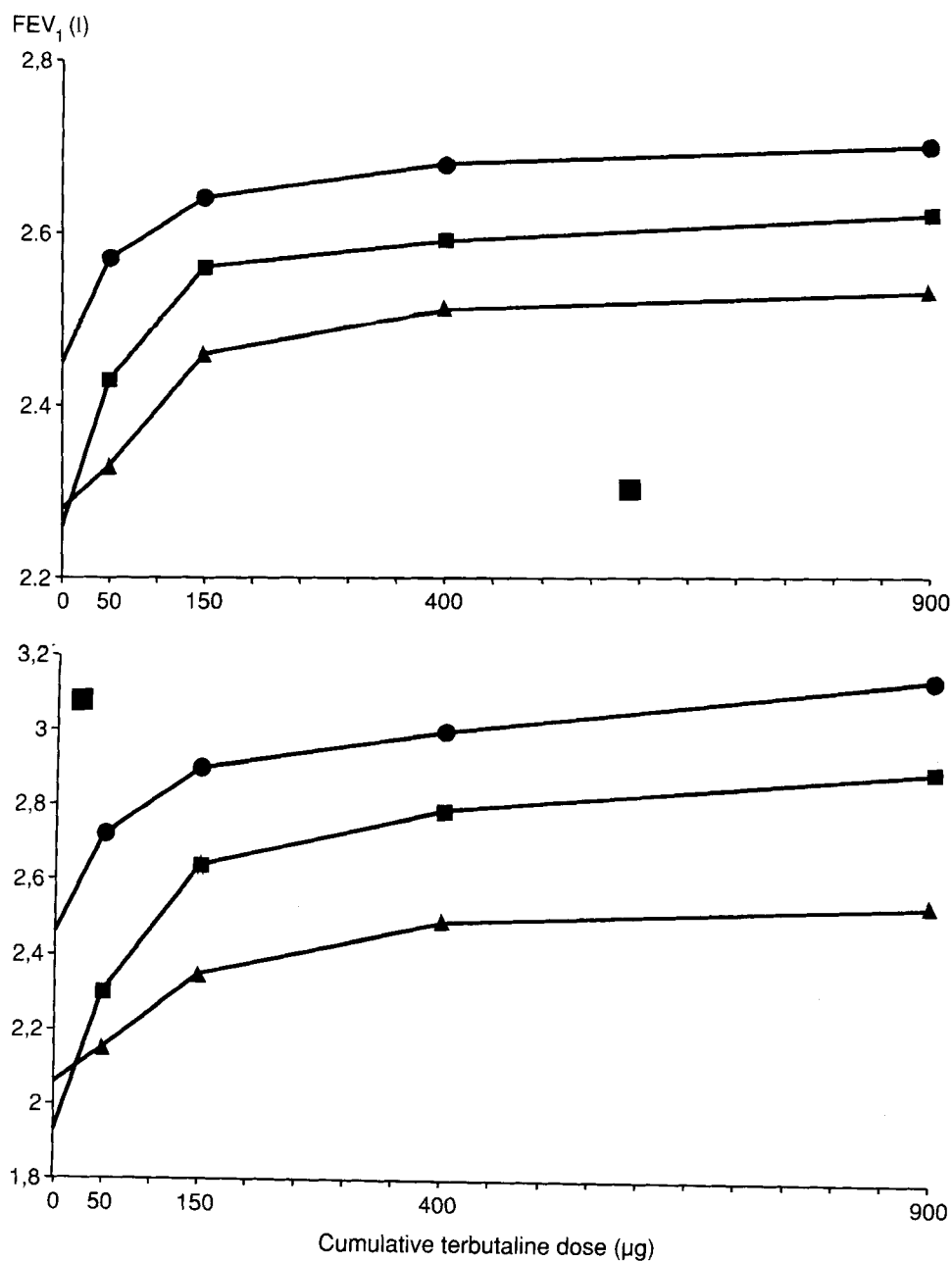


Fig. 1. FEV₁ and FEF₂₅₋₇₅ after inhalation of cumulated doses of terbutaline after 3 weeks' treatment with budesonide 100 µg twice daily (●), placebo (■) and salmeterol 50 µg twice daily (▲).

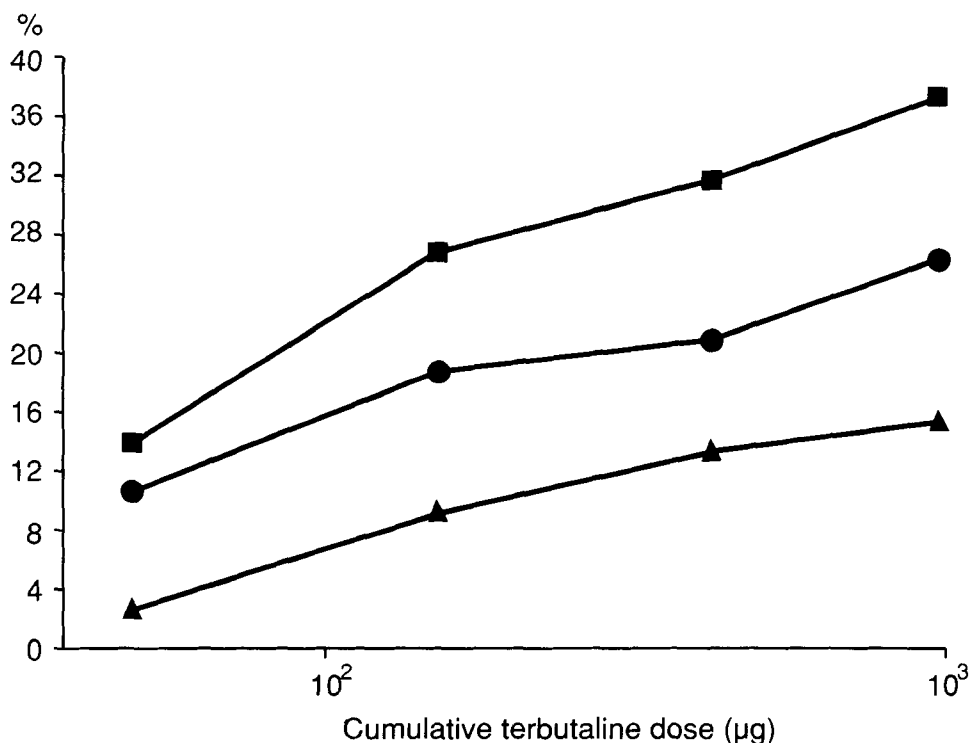
Diary recordings

There was no statistically significant difference in morning or evening PEF between salmeterol and budesonide treatment. Compared with placebo both active treatments resulted in a significant increase in morning PEF (increase after budesonide = 5.0%, $p=0.03$; after salmeterol = 5.6%, $p=0.003$). Salmeterol also caused a significant increase in evening PEF of 3.3% ($p=0.009$) compared with placebo whereas the increase in evening PEF after budesonide failed to reach statistical significance (2.1%, $p=0.10$).

Symptoms were mild or absent in all children during all 3 treatment periods. Compared with pla-

cebo (mean score = 0.70) budesonide significantly decreased asthma symptoms to a mean score of 0.41 ($p=0.02$). Furthermore, budesonide treatment improved the patient's well being from 0.46 (placebo) to 0.28 ($p=0.04$). Salmeterol did not change these parameters (mean symptom score = 0.63 ($p=0.22$) and mean well being score = 0.46 ($p=0.4$)). The use of rescue terbutaline was not significantly different between the three treatments (budesonide = 1.63, placebo = 1.66, salmeterol = 1.34 doses/week) ($p=0.44$).

Fig. 2. Per cent increase from baseline in FEF_{25-75} on a log-linear scale after inhalation of cumulated doses of terbutaline after 3 weeks' treatment with budesonide 100 µg twice daily (●), placebo (■) and salmeterol 50 µg twice daily (▲).



Discussion

Only patients assessed to have mild asthma were included in the study because we wanted to avoid too many treatment failures during placebo period and marked differences in baseline lung function between the two dose-response days. Furthermore, regular use of long-acting β_2 agonists without concomitant use of inhaled corticosteroids is most likely to be used in children with mild asthma. As a result of this patient selection a rather low bronchodilation was seen on the three test days. A priori it was decided that only the results from children who showed an increase from baseline of $\geq 25\%$ in FEF_{25-75} after inhaled cumulative terbutaline doses on the dose-response day after placebo treatment were included in the dose-response analysis. This criteria was fulfilled by 17 children. However, the conclusions from the whole group of children were identical to the conclusions derived from these 17 children i.e. a vertical upwards shift of the dose-response curve after budesonide treatment with a significantly higher E_{max} value and a statistically significant downward shift after salmeterol treatment with an E_{max} which was significantly lower than E_{max} after placebo.

There were too few data points in the middle part of the effect/concentration curve to permit reliable use of the E_{max} model or Hill equation with assessment of the slope of the curve by calculation of the S-parameter as we did in the earlier study (6). In that study terbutaline was administered intravenously.

This caused a much more gradual increase from baseline with small increments at each dose step. It would require much lower doses of inhaled terbutaline than used in the present study to achieve this. Therefore, it was not possible to accurately verify the hypothesis that inhaled budesonide can change the steepness of the dose-response curve to terbutaline. However, the results strongly suggested that budesonide did not potentiate the bronchodilating effect of terbutaline. It merely caused an increase in baseline lung function and a vertical shift of the curve. This indicates that the effect is additive – probably due to reduction of the oedema of the airways. This finding is in agreement with results of Henriksen (8), who found an additive and not a potentiating effect of budesonide and terbutaline in the protection against EIA (8) and the results of Wempe (9), who found that corticosteroid treatment did not enhance the response to a β_2 agonist but instead had an additive effect on bronchodilation and protection against histamine. These authors studied the effect of ongoing budesonide treatment and systemic prednisolone versus placebo treatment.

The optimal length of the treatment period is not known. However, the treatment duration with budesonide was sufficient to cause significant changes in baseline lung function. Therefore, we do not believe that a longer treatment period would have changed the conclusion. Furthermore, three weeks of salmeterol treatment also seemed to be sufficient to induce a significant change in the dose-response curve.

The results of the dose-response experiment after salmeterol treatment were surprising. It seemed as if salmeterol caused a downward shift in the terbutaline dose-response curve, so that the curve was less steep and the maximum response significantly reduced. The reason for this is not clear. There are several possibilities. 1) Since the salmeterol treatment was not randomized, a period effect can not be excluded. This was not observed in the double-blind part of the study. Furthermore, baseline lung function after salmeterol treatment was similar to placebo, indicating that the conditions were the same on the two various test days. 2) Salmeterol is a partial agonist. If the drug was still occupying the receptors when the dose-response experiment started, this could reduce the effect of terbutaline. The duration of action of salmeterol may extend beyond the 14–17 h which elapsed from the last dose in the present study. However, if this explanation is correct one would have expected baseline lung function to be higher than during placebo and that was not the case. 3) Down regulation of the β_2 receptors by the continuous treatment could also explain the finding of an unchanged baseline lung function and a reduced effect of terbutaline. This is in contrast with other studies which only suggest the development of tachyphylaxis against the protective effect of salmeterol against various challenges (10, 11) not against the bronchodilatory effects (12). However, the findings of a reduced response is in accordance with the results of two recent studies which both reported a significant reduction in bronchodilator response after continuous treatment with formoterol twice daily for 4 weeks (13, 14). To our knowledge no other dose-response studies have been performed in children to assess the risk of an attenuated bronchodilator response.

Even if the children suffered from mild asthma both active treatments significantly improved symptoms and peak expiratory flow rate measured at home without any significant difference in clinical effect between salbutamol and budesonide. So, on the basis of a clinical trial alone it could be assumed that one drug had no preference to the other. However, when findings in the dose-response experiments are considered the issue becomes more complicated.

With the reservations mentioned above we conclude that budesonide treatment does not enhance the bronchodilator response to terbutaline in chil-

dren with mild asthma. Further studies are needed to assess if long term treatment with salmeterol reduces the response to terbutaline.

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