

Simplification of Inhalation Therapy in Asthmatic children

A Comparison of Two Regimes

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In a placebo-controlled double blind cross-over study of 3 × 3 weeks' duration the effectiveness of a new set of simple instructions for the use of spacer aerosols was compared with that of the rather complicated manufacturer's instructions in the daily treatment of 22 children with severe asthma. All children received inhaled budesonide and terbutaline at the lowest dose possible for satisfactory symptom control. Both the simple and complicated regimes were significantly better than placebo ($P < 0.01$), but there was no indication that the complicated regime was superior to the simple regime. On the contrary, the children used significantly more rescue terbutaline and experienced more daytime symptoms when treated according to the complicated regime ($P < 0.01$). 19 of 21 children who completed the study preferred to use the simple regime ($P < 0.01$). It is concluded that instructions for the use of spacer aerosols should be substantially simplified and that conclusions from laboratory studies should be tested in the day-to-day management of asthmatics before these aerosols become widely used.

Key words: asthma; children; inhalation technique; tube spacer aerosols.

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Pressurized aerosols with tube spacers were designed to make inhalation therapy easier and more effective for asthmatic patients who have problems with the correct use of ordinary aerosols. However, even with tube spacers many children still fail to benefit sufficiently from this form of therapy (9). It is our impression that one of the major reasons for this is that the instruction leaflets contain so many guidelines about the correct use of the device that many children find them hard to understand and remember. Therefore, improving the success of inhalation therapy is not only a matter of developing new inhalers but also of making the instructions and methods of inhalation as simple and effective as possible.

To this end we have made laboratory evaluations of the impact on bronchodilator response of many of the instructions normally given in the manufacturer's leaflets about correct aerosol

use (8), and on the basis of these studies we have developed a set of simplified instructions which we hope will facilitate teaching and improve the success of inhaled therapy.

The aim of the present study was to evaluate whether these new simple instructions for inhaler use are as effective as the more complicated guidelines currently used in the day-to-day treatment of asthmatic children with moderate and severe asthma.

PATIENTS AND METHODS

Fifteen boys and seven girls, aged 6 to 15 years (mean 10.8 years) participated in the study. All suffered from perennial bronchial asthma to such a degree that they received regular inhalation therapy with corticosteroids and beta-2 stimulants. The duration of asthma symptoms varied from 4 to 13 years (mean 8 years). All

children had demonstrated a perfect inhalation technique on several occasions during the year prior to the trial.

The study was approved by the Ethics Committee of Northern Jutland, and informed consent was obtained from all children and their parents.

Before entering the trial the treatment of all children had been adjusted to the lowest dose of inhaled corticosteroid budesonide sufficient to control asthma symptoms satisfactorily when given twice daily. In the trial this dose was used morning and evening, preceded by inhalation of two puffs of terbutaline (0.5 mg). All children used pressurized aerosols with 10×3 cm tube spacers.

Two sets of guidelines were compared with each other and with placebo.

Guidelines A (current instructions). Treatment according to these instructions was given using white aerosols marked 1 (containing terbutaline/placebo) and 2 (containing budesonide/placebo). The following instructions were given:

- 1) Shake the canister
- 2) Place the lips around the mouthpiece
- 3) Exhale deeply through the inhaler
- 4) Tilt the head back
- 5) Actuate
- 6) Inhale as slowly and deeply as possible
- 7) Hold the breath for 10 seconds
- 8) Exhale through the nose

When the white aerosols were used the child took one puff of terbutaline/placebo (aerosol 1), waited 3 min before taking another puff, followed by a 3-min pause before taking the prescribed dose of budesonide/placebo (aerosol 2).

Guidelines B (new instructions). Treatment according to these instructions was given using brown aerosols (marked 1 and 2) *without any pause* between the various puffs of medicine. In addition, steps 3, 4, 7, and 8 from guidelines A were omitted.

The design was that of a controlled double blind, double dummy cross-over study of 3×3

weeks' duration where, at home, the children received in randomized sequence:

- active medicine in the white aerosols (terbutaline in 1 and budesonide in 2) and placebo in the brown aerosols (guidelines A)
- active medicine in the brown aerosols (terbutaline in 1 and budesonide in 2) and placebo in the white aerosols (guidelines B)
- placebo in both white and brown aerosols (placebo)

The study medicine was taken twice daily (morning and evening).

To facilitate the rather complicated regime, a flow chart of illustrative drawings on the left-hand pages of a diary took the child, step by step, through the whole medication procedure. A child was not included in the study until he/she had demonstrated a correct regime, with both white and brown aerosols, on two separate visits to the clinic. The results were only evaluated if the child used the inhalers correctly at each visit during the study. Apart from the study medicine the children used a blue terbutaline aerosol as rescue medication. No other drugs were used during the trial.

In the diary the child recorded *symptoms at night* (graduated from 0-4) according to written guidelines), *symptoms during the day* (0-5 according to written guidelines), *numbers of additional puffs of terbutaline* from the rescue aerosol and *peak expiratory flow rate (PEF)* (best of three) on a Mini-Wright peak flow meter before medication and 15 min after the last puff of medicine morning and evening. Finally, the occurrence of *side effects* was recorded.

Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), forced mid-expiratory flow rate (FMEF) and PEF were recorded at the hospital on a dry wedge spirometer (Vitalograph) with a function analyser, before the trial and at the end of each study period. These measurements were always taken at the same time of day. After the trial the children were asked whether they preferred guidelines A or B.

To avoid too severe deterioration of symptoms a period was judged a "treatment failure" if

two of the following four criteria were fulfilled on 3 consecutive days:

- 1) Diurnal variation in PEF $\geq 30\%$
- 2) A $\geq 30\%$ fall in PEF measured before morning medication as compared with the child's normal morning PEF.
- 3) Use of rescue terbutaline > 10 puffs/day.
- 4) Additional treatment with theophylline, beta-agonists or steroids was required.

When treatment failure occurred, further inhalation of the study medicine was stopped, and the child's normal treatment was resumed for 1 week. Thereafter, the child continued with the next study period.

Only the results from the last 2 weeks of each treatment period were studied.

Statistics

The data were evaluated by the method for cross-over trial designs (4). On all occasions, neither period nor carry-over effects were found.

Pulmonary function measurements at hospital were evaluated by Friedman's test as described by Conover (1). Wilcoxon's signed rank test was used to compare the results of the home recordings from the two active treatments and to find confidence limits (1). The patient's preference of regime was evaluated using the sign test.

RESULTS

One boy was withdrawn from the study due to his admission to hospital with continuous high fever of 3 weeks duration. The results from the remaining 21 children were studied.

Seventeen children did not complete the placebo period due to treatment failure (6 dropped out during the 1st week, 6 during the 2nd and 5 during the 3rd). No cases of treatment failure were observed during the active treatment periods. The condition of the four children who did complete the 3 weeks on placebo all deteriorated somewhat during the period: all used more rescue medicine, and had lower PEF and higher symptoms scores during the last week of the period than during the first week.

Morning PEF varied from 40% to 100% of the predicted value (mean 76%). There were no significant differences between the two active periods in morning PEF, increase in morning PEF after treatment, evening PEF, increase in evening PEF after treatment, diurnal variation in PEF, or the occurrence of symptoms at night (Table 1 and Fig. 1). However, daytime symptom scores were higher and the children used rescue terbutaline aerosols more frequently during treatment with the old technique than during the period with the new technique (Table 1). This difference was mainly due to rather substantial differences in these parameters recorded during the 3rd week of the two test-treatment periods (Fig. 2).

Table 1

Mean results from the last 2 weeks of home recordings. For the first two variables the relative difference is given ((New - Old)/Old) and for the last six the absolute difference is shown (New - Old). Diurnal variation was calculated as difference between evening and morning PEF in per cent of morning PEF

	Old technique	New technique	Difference (95% confidence limits)
Morning PEF (1/min)	306	305	0.01 (-0.02 to +0.05)
Evening PEF (1/min)	326	325	0 (+0.03 to +0.03)
Increase in PEF, morning (%)	13	15	2 (-2 to +3)
Increase in PEF, evening (%)	9	11	2 (+1 to +4)
Diurnal variation in PEF (%)	8	8	0 (-4 to +2)
Symptoms at night (0-4)	1.3	0.9	-0.4 (-1 to +0.25)
Daytime symptoms (0-5)	3.0	2.1	*-0.9 (-1.8 to -0.3)
Rescue terbutaline (puffs)	16	9	*-7 (-10 to -4)

* $P < 0.01$

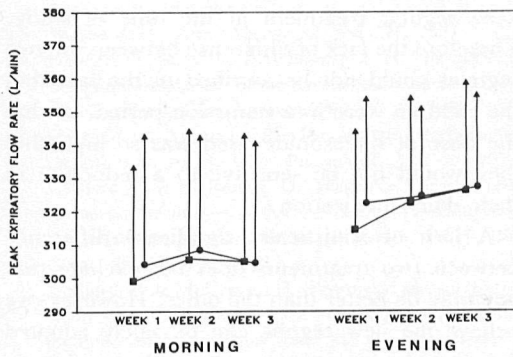


Fig. 1. Mean peak expiratory flow in the morning and the evening. ● = treatment with the old complicated technique. ■ = treatment with the new simplified technique. Arrows show the increase in PEF after two puffs of terbutaline.

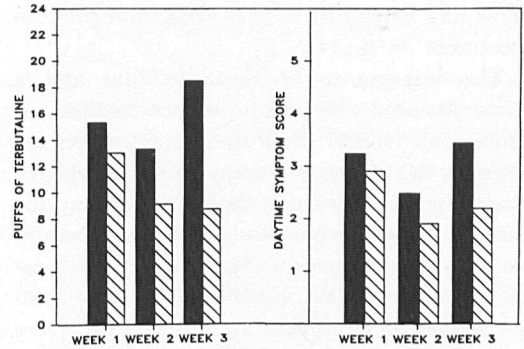


Fig. 2. Mean weekly use of rescue terbutaline and mean weekly daytime symptom score. ■ = treatment with the old complicated technique. ▨ = treatment with the new simplified technique.

There was no statistically significant difference between the old and the new technique in pulmonary functions in hospital at the end of each period (Table 2). However, both active treatments were significantly better than placebo and FEV₁ measurements were better than the pre-trial measurements.

The conclusions were the same, whether the results from the four patients who completed the placebo period were discounted or if the results from all 3 weeks, or only the last two, were compared.

Nineteen children preferred to use the new guidelines, one preferred the old regime, and one had no preference ($P < 0.1$). No side effects were reported.

DISCUSSION

Various investigators have studied inhaler technique in adults (2, 3, 5, 6, 7, 11, 12, 13). These studies have been conducted under laboratory conditions, using either bronchodilation or pulmonary deposition of radiolabelled teflon particles to measure the effectiveness of the treatment. The studies have differed in design and inhaler used, and the results have been contradictory. Therefore we wanted to evaluate the clinical importance of some of these laboratory findings in children treated with inhaled corticosteroids and beta-2 agonists.

It has earlier been found that tilting the head back during inhalation does not improve the response (8), and many studies have failed to

Table 2

Mean pulmonary function measurements at hospital before study and at the end of each treatment period. If a child dropped out during the placebo period the spirometric data obtained on the last day of treatment were used for analysis

	Predicted	Before study (O)	Placebo (P)	Old technique (A)	New Technique (B)	Friedman's test
FEV ₁ (l)	2.91	2.15	1.70	2.26	2.35	$P^* < O^* < A < B$
FVC (l)	2.25	2.83	2.42	2.92	2.98	$P^* < O < A < B$
FMEF (1/s)	3.49	2.31	1.33	2.15	2.37	$P^* < A < O < B$
PEF (l/min)	3.45	292	212	297	310	$P^* < O < A < B$

* $P < 0.01$

show any benefit of a deep exhalation prior to treatment (6, 8, 11).

The importance of breath-holding and a pause between two puffs of a bronchodilator is more controversial. Both these manoeuvres are tiresome and impede therapy to such a degree that their clinical benefit should be without dispute. So far only one study has found breath-holding to be important (7). However, the beneficial effect was only significant when the aerosol was actuated during the last half of a very slow inhalation and not when actuated early, or with fast inhalations. As in the present study, other investigations have not found breath-holding to have any beneficial effect (5, 8). In addition, the results of our study did not confirm that a pause between puffs was of any clinical advantage in the routine day-to-day management of asthmatic children. This is in accordance with the findings of some laboratory studies and a recent clinical trial (2, 6, 10, 12) but opposed to the results of other laboratory studies (3, 11). It is possible, however, that a short pause between puffs may improve bronchodilation during episodes of acute wheezing or periods of bad symptom control and low baseline pulmonary functions (10).

The terbutaline dose given by us was that normally recommended for clinical use. As this dose probably contains more than enough drug to produce maximal bronchodilation, it is possible that the results would have been different if lower doses had been used. In that case, however, the conclusion might not have been clinically relevant.

As, to our knowledge, exhaling through the nose has never been shown to improve effect, many of the manufacturer's current instructions could be safely omitted without any significant loss of effect in the day-to-day management of asthmatic children. This is important as the simpler the instructions the more likely they are to be fully understood and carried out.

Before the trial the dose of budesonide had been individually adjusted to a dose low enough to control the child's symptoms and during the study most children on this dose did experience some symptoms. In addition, the placebo period demonstrated that the children really did

need regular treatment at the time of study. Therefore the lack of difference between the two regimes could not be ascribed to the fact that the children were in a remission period, or that the dose of budesonide used was so high that they would not be sensitive to a reduction in their daily medication.

A lack of statistically significant difference between two treatments does not exclude that one may be better than the other. However, we believe the new regime can be safely adopted for clinical use, as in our study the confidence limits of the relative differences between peak flow measurements showed little risk ($< 2.5\%$) of the new technique being more than 2% worse than the old one.

It may be a coincidence that with the old technique the children used terbutaline more frequently and experienced more daytime symptoms than with the new technique, but this could be because the children found the old technique more cumbersome and difficult to follow. The latter suggestion was supported by many of the parents who had noticed that, with the old regime, the children needed more supervision or else they would scamp medication or forget a puff.

Conclusion

Instructions for the use of spacer aerosols can be substantially simplified without any clinically important loss of effect. Such a simplification would facilitate instruction, reduce the conflicts between many asthmatic children and their parents about medication, and, hopefully, improve compliance.

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