

Clinical efficacy of budesonide Turbuhaler® compared with that of beclomethasone dipropionate pMDI with volumatic spacer

A 2-year randomized study in 102 asthma patients

Selroos O, Backman R, Forsén K-O, Löfroos A-B, Niemistö M, Pietinalho A, Riska H. Clinical efficacy of budesonide Turbuhaler® compared with that of beclomethasone dipropionate pMDI with volumatic spacer. A 2-year randomized study in 102 asthma patients. Allergy 1994; 49: 833–836. © Munksgaard 1994.

A total of 102 patients had their asthma treatment with beclomethasone dipropionate (BDP) optimized in order to achieve the best possible control of symptoms. Thereafter, the BDP doses were gradually reduced over a 2-year period (1988–90) to the lowest possible without deterioration of their asthmatic condition. In the beginning of 1990, treatment was changed in 76 patients (group A) to the nearest possible dose of budesonide delivered via Turbuhaler®. Twenty-six randomly selected patients (25% of the study population; group B) continued treatment with BDP. In both groups, dose reductions were tried during 1990–2 every third month as long as the patients remained symptom-free and without significant decreases in FEV₁ or PEF. In group A, the maintenance dose could be reduced from 1003.9 ± 325.4 µg BDP (mean $\pm$ SD) to 602.9 ± 454.4 µg budesonide Turbuhaler ($P < 0.001$). In group B, no significant dose reduction was possible; the mean dose was $\pm$ SD 1067.3 ± 36.6 µg in 1990, and 1019.2 ± 324.7 µg in 1992. The results indicate that, in efficacy, 0.6 mg budesonide Turbuhaler corresponds to approximately 1.0 mg BDP with volumatic spacer. This difference is probably due to an improved pulmonary delivery of budesonide with Turbuhaler.

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Key words: beclomethasone dipropionate; budesonide; glucocorticosteroids; inhalation therapy; powder inhaler; pressurized aerosol; spacer device.

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Accepted for publication 31 March 1994

Inhaled corticosteroids (ICS) have been used for more than 20 years to treat bronchial asthma. At first, they were used for patients who otherwise would have been treated with oral steroids. They were also used in low and fixed doses, the standard dose of beclomethasone dipropionate (BDP) being 100 µg four times daily.

The information gained over time on the efficacy and safety of ICS has resulted in their increased use. Today, ICS are given as first-line therapy to patients with newly detected asthma of all types of severity, including mild cases (5). Guidelines for treatment of asthma also recommend early intervention with ICS to achieve normal or the best possible level of airway function (3, 7). Thereafter, the dose of ICS should be individually adjusted to the lowest possible dose which keeps the patient on the level of achieved asthma control.

In the late 1980s, we started to optimize the doses of BDP pMDI (pressurized metered-dose inhaler),

given via a large-volume spacer. Patients not well controlled received increasing doses of BDP, up to 2500 µg a day, until the best possible level of airway function and symptom control had been identified. Thereafter, we titrated the dose on an individual level to the lowest possible, as mentioned above. If symptoms developed on a reduced dose, or the peak expiratory flow (PEF) decreased by 10% or more (or by 50 l/min or more), the dose was increased to the previous level.

In clinical efficacy, BDP and budesonide delivered via pMDI with or without large-volume spacers have been found to be equally effective in nominal doses (6). In 1990, budesonide in Turbuhaler® – an inspiratory-flow-driven, multi-dose powder inhaler – was introduced. For evaluation of the new inhaler, a group of patients was given budesonide Turbuhaler instead of BDP with spacer. This report deals with results obtained in the management of asthma after optimizing treatment with BDP during

a period of 2 years, and, thereafter, in comparing BDP, with volumatic spacer, with budesonide Turbuhaler during a further 2-year period with respect to clinical efficacy.

Material and methods

Patients

Group A (study group). Group A comprised 76 patients with bronchial asthma, 28 men and 48 women. Their mean age was 50.7 ± 16.2 years. They had had asthma for a mean of 7.2 ± 5.5 years and had been treated with BDP with volumatic spacer for a mean of 5.1 ± 4.3 years. During 1988–90, their BDP mean dose $\pm$ SD had been reduced to 1003.9 ± 325.4 μ g a day. When their treatment was changed to budesonide Turbuhaler, they had a mean PEF value of 365.3 ± 136.3 l/min (mean $\pm$ SD), corresponding to $77.0 \pm 22.9\%$ of the predicted normal value.

Group B (control group). Group B comprised 26 patients with bronchial asthma, 10 men and 16 women, mean age 47.9 ± 15.1 years. They had had asthma for a mean of 6.5 ± 4.9 years (mean $\pm$ SD), and they had used BDP with volumatic spacer for a mean of 4.2 ± 4.0 years.

Early in 1990, when group A patients were changed to treatment with budesonide Turbuhaler, group B patients had a mean dose of BDP of 1067.3 ± 306.6 μ g daily (not significantly different from the mean dose of group A). Their mean PEF value at that time was 362.9 ± 140.8 l/min, corresponding to $75.5 \pm 23.7\%$ of predicted normal values.

Study design

The study was an open, randomized, parallel-group study. By means of a computer-generated randomization in blocks of four, three of four patients received budesonide Turbuhaler, and one patient continued treatment with BDP pMDI and spacer.

Visits and asthma management

The patients visited the outpatients' department at 3-month intervals. If the dose was reduced, patients were asked to contact the hospital immediately if asthma symptoms became worse or if PEF decreased by 50 l/min or more.

At hospital visits, patients were asked about symptoms and adverse experiences of the drugs. Their throats were inspected for diagnosis of clinical *Candida* infection. Spirometry was done with a Vitalograph® compact spirometer (Vitalograph Ltd, Buckingham, UK).

The patients used either a BDP pMDI with volumatic spacer, which delivered 250 μ g per actuation,

or budesonide Turbuhaler delivering a nominal dose of either 200 μ g or 400 μ g per inhalation. A reduction of dose was always 250 μ g BDP or 200 μ g budesonide. All treatments were given twice daily.

Patients changing treatment from BDP pMDI to budesonide Turbuhaler received a dose which was the same as, or as close as possible to, the dose of BDP. For example, patients on 1000 μ g BDP received 1000 μ g budesonide Turbuhaler; patients on 1500 μ g BDP received 1600 μ g budesonide. All doses of ICS were determined on an individual basis. No fixed scheme for dose reductions was used. A dose reduction was attempted if the patient was completely, or almost, symptom-free and the airway function (PEF and FEV₁) was on the same level as at the previous visit. No dose reduction was permitted if PEF or FEV₁ had decreased by 10% or PEF by 50 l/min from the value at the previous visit. On the contrary, if such a deterioration had occurred, the dose was increased instead.

Statistics

Paired *t*-tests were used to compare changes in lung function values and doses of drugs.

Results

Dose reduction

Group A. When treatment was changed from BDP pMDI to budesonide Turbuhaler, the patients had a mean dose of BDP of 1003.9 ± 325.4 μ g. They were changed to a mean dose of budesonide of 950.0 ± 351.1 μ g daily, which was given via Turbuhaler. During the 2-year follow-up period, it was possible to reduce the dose to a mean of 602.9 ± 454.4 μ g (Fig. 1). This dose reduction was statistically significant ($P < 0.001$). A dose reduction was possible in 41 patients, the dose remained unchanged in 24, and the dose had to be increased in 11 patients.

Group B. In the control group, the mean daily dose of BDP pMDI was 1067.3 ± 306.6 μ g when group A patients changed their medication to budesonide Turbuhaler. During the 2-year follow-up period, it was possible to reduce the dose in four cases. The dose remained unchanged in 19 and had to be increased in three patients. The mean maintenance dose at the end of the study was 1019.2 ± 324.7 μ g daily. The reduction of dose during the 2-year period was not statistically significant.

Concomitant asthma medication

During the study period, it was possible to reduce the concomitant asthma medication. This happened

mainly with inhaled β_2 -agonists, when well-controlled patients changed treatment from regular to on-demand use. In group A, all 76 patients used an inhaled β_2 -agonist on a regular basis when changing treatment from BDP to budesonide Turbuhaler. Two years later, the figure was 55. In group B, the corresponding figures were 26 and 21, respectively. The difference between the groups was not significant. There were few changes in other concomitant medications and never more reductions in percentage in group B than in group A.

Lung function data

Spirometry results of both groups, obtained when group A patients changed treatment from BDP pMDI to budesonide Turbuhaler and at the last visit, are shown in Table 1. No differences between the groups were found. Slight, statistically nonsignificant increases in PEF values were noted. FEV₁ values remained at the same level. The mean doses of drugs used and the corresponding PEF values are illustrated in Fig. 1.

Acute attacks of asthma

The number of acute attacks of asthma was recorded. In 1988, there were 2.7 attacks per patient and year in group A, and 4.0 in group B. Thereafter, the number of attacks decreased in both groups and remained around 1.0 per patient per year for the rest of the observation period. Almost 60% of the patients became free of acute attacks (Fig. 2).

Local side-effects

Group A. During 1988–90, local side-effects had been reported in 18 patients (23.6%); oropharyngeal candidiasis in two and hoarseness in 16. During treatment with budesonide Turbuhaler, four patients with local side-effects were seen (5.3%); one with candidiasis and three with voice problems. These four patients with local side-effects during treatment with Turbuhaler had had similar local side-effects during previous treatment with BDP with spacer.

Table 1. Results of lung function tests in 1990, when 76 randomly allocated patients (group A) changed treatment from BDP pMDI with volumatic spacer to budesonide Turbuhaler, and 2 years later (1992). Group B patients ($n=26$) continued treatment with BDP pMDI with spacer

		FEV ₁ (l)	FEV ₁ (% pred)	PEF (l/min)	PEF (% pred)
Group A	1990	2.33±0.92	72.0±22.3	365.3±136.3	77.0±22.9
	1992	2.35±0.92	74.8±23.6	379.5±131.5	81.6±25.8
Group B	1990	2.41±0.88	73.2±23.9	362.9±140.8	75.5±23.7
	1992	2.42±0.88	73.2±21.4	380.1±133.8	78.3±23.8

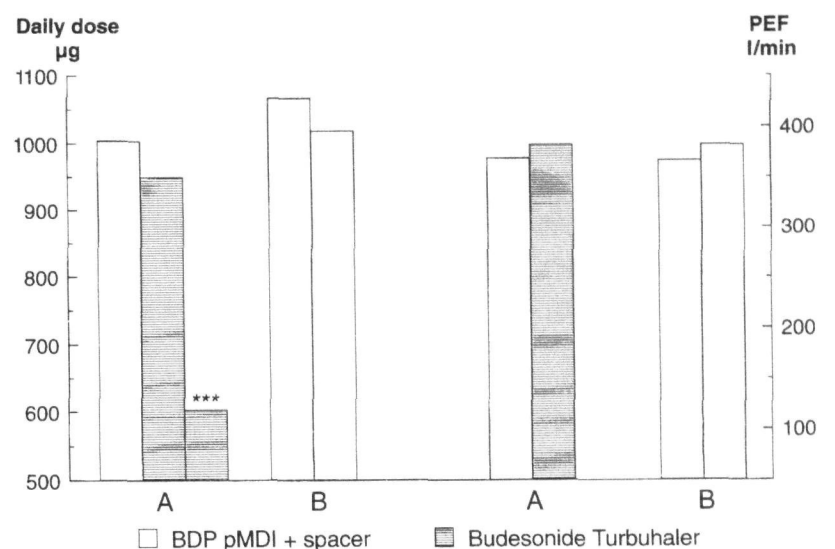


Fig. 1. Mean daily optimized doses of inhaled corticosteroids before changing treatment from beclomethasone dipropionate (BDP) to budesonide Turbuhaler (group A), or before continuing treatment with BDP (group B), and 2 years later. Dose reduction in group A was significant (***) $P < 0.001$. Mean PEF values obtained at same times are shown on right.

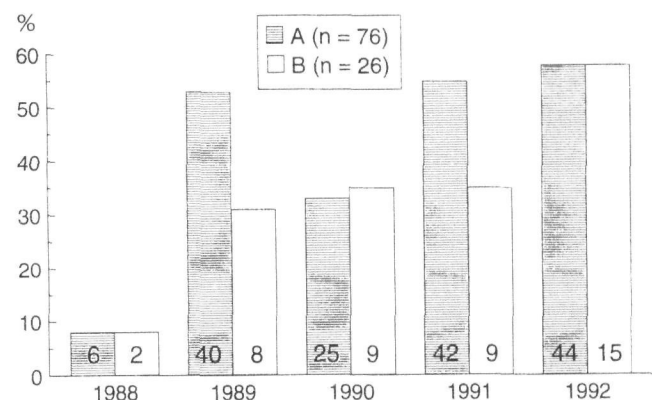


Fig. 2. Annual percentage of patients without acute attacks during 1988–92. Numbers in each bar represent number of patients in each group. Group A and group B as in Fig. 1.

Group B. The frequency of local side-effects did not change; 19.2% during the first 2-year period, and 15.4% during the second 2-year period (five and four patients, respectively, with hoarseness).

Discussion

Patients with asthma easily accept a suboptimal level of disease control, especially if some subjective improvements are felt with a new treatment over their previous situation. However, as soon as a high-dose regimen with ICS has been successfully applied, the patients find it hard to accept a return to a poorer level of asthma control. Therefore, it is wise to start treatment with ICS with fairly high doses to determine the best possible level of airway function and symptom control. In patients with a reasonably short duration of asthma, it is usually possible to obtain normal airway function in relation to predicted reference values.

In recent years, the need for individually adjusted doses of ICS to obtain the wanted efficacy, but also

to avoid unnecessary systemic side-effects with high doses, has been repeatedly addressed (4, 9).

In 1987–8, we realized that we were still tending to use fixed doses of ICS. We rarely tested whether a given dose was unnecessarily high or low. To achieve the best possible control, we started to optimize the doses of ICS during 1988–90. The most important thing was to try to reduce the daily dose to the lowest possible dose which kept the patient symptom-free and with a normal, or best possible, airway function. Changes in dose were not done more frequently than every third month. By doing this, we were able to determine the minimum effective dose in each patient. In early 1990, budesonide in Turbuhaler was made available. Because we were using an inhalation system without a spacer device, we feared an increased risk of local side-effects. We therefore decided to monitor the patients carefully when changing treatment from pMDI to Turbuhaler.

This study shows that, during a 2-year period, it was possible to reduce the dose of budesonide Turbuhaler from a mean of 950 µg (the mean dose of BDP pMDI was 1003 µg) to 603 µg, whereas no corresponding dose reduction could be obtained in patients continuing with BDP pMDI (1067 and 1019 µg).

The airway function, measured as FEV₁ and PEF, did not deteriorate in either group, indicating that the given treatment at the end of the follow-up period was as effective as in the beginning of the study. Moreover, the number of acute attacks of asthma and the percentage of patients without any acute attacks were the same in both treatment groups.

During the study, changes in concomitant asthma medications were possible. Reductions were seen in both groups, mainly as changes from regular to on-demand use of inhaled β_2 -agonists in patients well controlled on their current medication. The concomitant medications were not reduced more in the group continuing treatment with BDP. Therefore, the infeasible dose reduction in the control group cannot be explained as a consequence of reduction in concomitant medication.

The best explanation for the difference in daily nominal doses of BDP pMDI and budesonide Turbuhaler resulting in equal levels of clinical efficacy is the difference in lung deposition between Turbuhaler and pMDI. In their study in 24 subjects, Thorsson & Edsbäcker showed that Turbuhaler gave a lung deposition which was less variable than, and twice as much as, that from a pMDI (8). At the same time, Turbuhaler treatment halved the availability of budesonide from the gastrointestinal tract. Thus, there was a more beneficial ratio of local lung delivery to unwanted delivery at other sites.

We deliberately used an open-study design because a blinded study requires a double-dummy

method, which may seriously affect patient compliance during a 2-year study period. By using an open, but randomized design, we were able to keep all patients in the study for the entire study period.

The results of this long-term study agree with results obtained in other studies in children (1) and in adults with asthma (2). In the former, Agertoft & Pedersen (1) screened 241 children with asthma by halving their dose of budesonide pMDI with spacer. Children developing a 25% fall in PEF ($n = 126$) were included in a run-in phase during which they received their previous dose of budesonide, 400 µg or 800 µg daily, as pMDI with spacer. Thereafter, they were randomized to continued treatment with pMDI with spacer or to half the dose of budesonide given via Turbuhaler (200 µg or 400 µg daily). Half the dose given via Turbuhaler was clinically as effective as the full dose of budesonide given as pMDI via Nebuhaler® spacer. In the latter study, a 3-month randomized study in asthmatic adults, Brambilla et al. (2) tried to reduce the doses of BDP pMDI or budesonide Turbuhaler. The same level of asthma control was achieved at the end of the study with 1350 µg BDP pMDI as with 900 µg budesonide Turbuhaler. A 50% higher dose of BDP was thus required.

The results of this long-term study give further support to attempts to reduce maintenance doses of ICS to the lowest possible effective dose. The Turbuhaler delivery system seemed here to be better than a pMDI with spacer.

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