

A double-blind dose-response study of budesonide by inhalation in patients with bronchial asthma

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Budesonide by inhalation and placebo were tested in 18 patients with moderate chronic bronchial asthma. Three dose levels of budesonide were used (25, 100 and 400 µg q.i.d.) and the patients were to take two puffs q.i.d. in all periods. The active treatment was investigated using double-blind cross-over technique, and placebo at the end of the trial. The duration of each treatment period was 2 weeks. The study showed a high drop-out frequency while on placebo and that the PEF values were influenced in a dose-dependent way by budesonide. In spite of the double-blindness the patients had a tendency towards overuse of the trial aerosol on the lowest dose, but they used significantly less than prescribed during the period with the highest dose. No side effects were reported.

Key words: bronchial asthma; budesonide; compliance; dose-response; inhaled corticosteroid; treatment.

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During the last 10 years, inhaled corticosteroids (IC) have come into wide-spread use in the treatment of asthma, gaining a reputation of being both effective and without major adverse effects.

Although in use for nearly a decade, IC are still often used in a very standardized way, and the usual dose for most patients on inhaled beclomethasone dipropionate (BDP) is 100 µg q.i.d. When needed, oral corticosteroids are given in addition. The therapeutic ratio for IC, i.e. the relation between the topical anti-inflammatory and systemic effects, is considered to be better than that for oral corticosteroids (5, 8, 9), and although comparative dose-response studies between morning oral corticosteroids and IC are still lacking, it would be reasonable to take advantage of the good therapeutic ratio for IC and increase the dose of inhaled steroids before instituting oral steroid treatment.

Although a major step in the development of asthma treatment, BDP has in some instances given systemic effects also in the therapeutic dose range (7, 10, 11, 12).

Budesonide is a new synthetic corticosteroid that has shown an improved therapeutic ratio in animal (3) and man (6). Inhaled budesonide has also been shown to have an anti-asthmatic effect (2, 4, 8, 9).

The aim of the present study was to investigate the response curve for inhaled budesonide after daily doses of 100, 400 and 1600 µg in randomized order to patients with moderate to severe asthma. The dose-response relationship for BDP and budesonide in patients with more pronounced asthma has been reported previously (9, 10), although in these studies the doses were given in non-randomized order.

MATERIAL AND METHODS

Patients

The study was performed in 18 adult patients suffering from bronchial asthma as defined by the American College of Chest Physicians and the American Thoracic Society (1). None of the

patients was sufficiently controlled by bronchodilators (β -receptor agonists and/or methylxanthines) and DSCG but needed additional medical treatment. None of the patients had chronic bronchitis or a restrictive lung disease. Ten of the patients were female and eight male. The mean age was 46 (range 28–68) years and the mean duration of asthma was 19 (range 2–59) years. Prior to the study, 14 of the patients used inhaled BDP in a daily dose of 400 μ g.

During the study all patients were given a basal medication of β -receptor stimulants by inhalation and/or by mouth. Four patients used oral theophyllines and four used oral corticosteroids in a dose corresponding to 5–15 mg prednisolone/day. One patient used DSCG and one intranasal BDP. All drugs except inhaled β -receptor agonists were kept at fixed doses throughout the study.

The patients showed an improvement in PEF of $> 15\%$ within 30 min of two inhalations from a bronchodilator aerosol. Allergological investigations with skin prick test, RAST and allergen challenge had shown eight patients to have an allergic component of clinical importance to one or more of the following antigens: animal dander, house dust mite, pollens or moulds. Four patients were sensitive to aspirin and two to exercise. Eight patients had perennial rhinitis and one had urticaria.

Study design

The trial was performed as a double-blind placebo-controlled cross-over study, consisting of a 1-week run-in period to accustom the patients to the trial procedure. During this period the

patients inhaled beclomethasone dipropionate in a daily dose of 400 μ g (100 μ g q.i.d.), followed by three periods, each of 2 weeks' duration (a total of 6 weeks) during which the patients inhaled different doses of budesonide in randomized order.

The daily budesonide doses during the three treatment periods were 100, 400 or 1600 μ g divided in four parts and given by a non-spacer actuator as 25, 100 and 400 μ g q.i.d. Budesonide was inhaled from aerosols with identical formulation and appearance but with different concentrations of budesonide. The two higher doses were given with 50 μ l and the lowest with a 25 μ l valve. Two inhalations were given each time.

The study ended with a placebo period of up to 2 weeks' duration. Placebo was to be stopped if the morning PEF on 2 consecutive days was $\leq 80\%$ of the mean during the run-in period. If at any other time during the study a patient deteriorated so much that he/she was at risk of not remaining in the trial, this patient should be continued on the dose to be given in the following period.

Recording of effects

The patients recorded peak expiratory flow (PEF) with a mini Wright peak flow meter each morning after rising, but before using any drugs. PEF was measured again in the evening before going to bed, but after administration of the drugs. Three recordings were made each time. The highest value was noted in a diary card and used for statistical calculation.

The patients also gave their daily assessment of: a) breathlessness at rest, b) breathlessness after exertion, c) sleep disturbance caused by

Table 1

Mean daily number of inhalations of budesonide and real dose at the different intended dose-levels

	100 μ g/day		400 μ g/day		1600 μ g/day	
	No. inhalations	Dose μ g	No. inhalations	Dose μ g	No. inhalations	Dose μ g
$\bar{x}$	8.71 ^a	109	7.99 ^a	395	5.89 ^{***}	1178
SEM	0.99	12	0.67	34	0.42	84

*** $P < 0.001$ Difference vs intended No. of inhalations

^a $P < 0.05$ Difference vs 1600 μ g/day

asthma, and d) severity of asthma. The scores were given according to a scale where 0 indicated "well" and 10 "severe".

Bronchodilator aerosol was used to treat acute attacks and the number of inhalations was recorded daily by the patients in their diary card. The patients saw the investigator before the start of each new trial period and were invited to contact him at any time if they felt worse. Candida was looked for at each visit to the hospital, and the patients were encouraged to report any

side effects in the diary card. The budesonide aerosols were returned at the end of each period and weighed for control of drug consumption.

Statistical methods

Student's t-test for paired differences has been used and the mean of the recordings from the last 4 days per period, or before drop out, has been used for comparisons. The randomization was made in blocks so that each budesonide dose was equally represented during all three trial periods.

Ethical aspects

The study was performed in accordance with "the Declaration of Helsinki" and informed consent was obtained from all participants before the onset of the trial. The study was approved by the Danish health authorities.

RESULTS

Eighteen patients participated in the trial. However, in the placebo period PEF is calculated in

Table 2

PEF (l/min) in the morning in the different treatment periods (M $\pm$ SEM, n = 18)

Drug/dose μ g	M $\pm$ SEM
Run-in	306 $\pm$ 19
Budesonide 25 q.i.d.	300 $\pm$ 27
Budesonide 100 q.i.d.	319 $\pm$ 23
	*aa
Budesonide 400 q.i.d.	334 $\pm$ 23
Placebo	308 $\pm$ 30

*P < 0.05 Difference vs placebo

aaP < 0.01 Difference vs Bud 25 μ g q.i.d.

Table 3

The patients' rating of the asthma during the different treatments. (M $\pm$ SEM, n = 18)

	Run-in	Budesonide μ g/day			
		100	400	1600	Placebo
Breathlessness			a **	a *	
at rest	1.56 $\pm$ 0.32	1.89 $\pm$ 0.42	0.94 $\pm$ 0.3 a *	1.27 $\pm$ 0.33 aaa *	2.37 $\pm$ 0.63
on exertion	2.70 $\pm$ 0.49	2.83 $\pm$ 0.39	1.71 $\pm$ 0.43 a **	1.98 $\pm$ 0.42 *	3.06 $\pm$ 0.68
Sleep disturbances caused by asthma	1.59 $\pm$ 0.26	2.18 $\pm$ 0.48	1.27 $\pm$ 0.33 a ***	1.41 $\pm$ 0.40 aa	2.98 $\pm$ 0.78
Asthma severity score	2.73 $\pm$ 0.41	3.03 $\pm$ 0.38	1.8 $\pm$ 0.40 *	2.25 $\pm$ 0.41	3.41 $\pm$ 0.62
Daily number of extra bronchodil. inhalations	3.61 $\pm$ 0.56	3.82 $\pm$ 0.76	2.74 $\pm$ 0.61	3.54 $\pm$ 0.68	5.31 $\pm$ 0.83

* P < 0.05

** P < 0.01 } Difference vs placebo

*** P < 0.001

a P < 0.05

aa P < 0.01 } Difference vs budesonide

aaa P < 0.001 } 100 μ g (25 μ g q.i.d.)

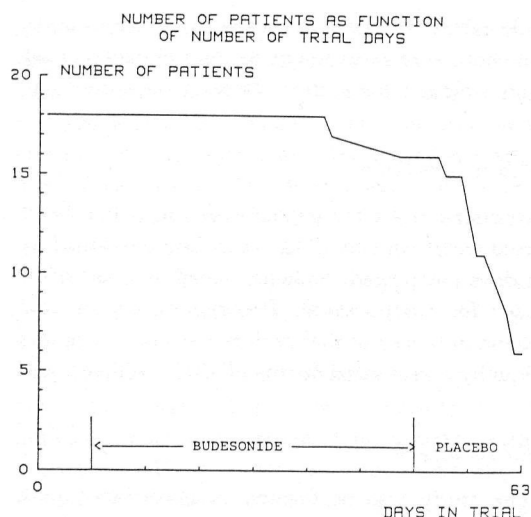


Fig. 1. The number of patients as a function of treatment time. The decrease during the last part of the budesonide period was due to drop-out of two patients on 25 µg q.i.d.

16 patients as two patients dropped out during the third period with budesonide. Both patients used the lowest dose of budesonide (25 µg q.i.d.) in this period, and they are both included in the analysis of this dose level. The number of patients as a function of time in the trial is shown in Fig. 1.

The number of patients for whom scores are given is lower because some patients did not give subjective scores for all parameters.

Use of trial aerosols

The prescribed dose was in all periods 8 inhalations/day. During the period with 100 µg q.i.d. (middle dose) the observed use and expected use were almost identical. In the period with the lowest dose there was a non-significant tendency to increase the daily number of inhalations, and when on the highest dose there was a statistically significant difference between real use and prescribed use. Use during the high-dose period was also lower than during both other periods (Table 1).

Peak expiratory flow (PEF)

A dose-dependent variation in PEF was found both morning and evening (Table 2, Fig. 2).

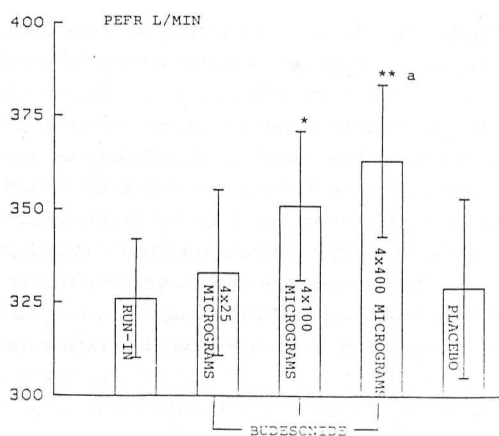


Fig. 2. PEF (l/min) in the evening in the different treatment periods ($M \pm SEM$, $n = 18$).

* $P < 0.05$
** $P < 0.01$ } Difference vs placebo

a $P < 0.05$ Difference vs budesonide 25 µg q.i.d.

When comparing the morning PEF values, only those after the highest dose of budesonide were significantly different from placebo, but in the evening also the middle dose and placebo were significantly different.

Subjective evaluation

The patients' symptom scores for breathlessness at rest and on exertion showed that the two highest doses of budesonide were superior to placebo and the lowest dose of budesonide (Table 3).

The patients' evaluation of sleep disturbances caused by asthma showed budesonide 400 and 1600 µg/day were superior to placebo, and 400 µg daily was superior to 100 µg (Table 3).

The score for asthma severity showed that budesonide 400 and 1600 µg/day were superior to 100 µg daily, but only a daily dose of 400 µg budesonide was statistically different from placebo (Table 3).

When calculating the number of inhalations from bronchodilator aerosols during the trial, only budesonide 400 µg/day had a significantly lower value than placebo (Table 3). Candidiasis

and hoarseness were not reported during the study.

DISCUSSION

There was a high drop-out rate during the placebo period (Fig. 1). This strongly indicates that all dose-levels tested were more effective than placebo, but it created a problem for statistical evaluation – either those patients who dropped out had to be omitted from the statistical analysis between placebo and the active treatments or had to be included using a value obtained before they dropped out. If the first choice was made it would, in the extreme, result in comparing a treatment with placebo in patients who were so stable in their asthma that they could tolerate the substitution of corticosteroids with placebo for at least 2 weeks, or perhaps they were in no present need of the investigated treatment at all. Whatever the reason, this choice would probably overestimate the relative effect of placebo as an alternative to inhaled corticosteroids.

If, however, data for the patients who dropped out were used for statistical comparison with the value obtained before they dropped out, this could also result in an overestimation of the effect of placebo, as the measured values would be residual effects from the previous active treatment. Although far from ideal, we found this second alternative better and decided to include all patients in the statistical analysis in treatment periods in which they had participated for at least 4 days. For comparison between treatments we used the mean of the last 4 days per treatment period for each individual, or the mean of the last 4 days before a patient dropped out. The last 4 days of a 2-week period were used as it has been reported previously that when treated for 2 weeks the effect-plateau was usually reached within 10 days (2). The mean of the last 4 days was used, as this reduced the SD substantially more than when the last day or the mean of the last 2 or 3 days was used.

This study showed inhaled budesonide to have a dose-dependent anti-asthmatic effect, even the lowest dose giving some protection.

These results are in conformity with those from the non-prednisone users in a study by Toogood et al. (9), whereas the prednisone users in the same study needed a higher dose to obtain the same improvement in lung function. A direct comparison between the two studies is hard to make because of the difference in method, but nevertheless the similarity in results is striking, and both studies clearly demonstrate that the dose of inhaled budesonide should be individualized to give optimum benefit to the patients.

The deviation from the prescribed dose while on the high dose is probably due to a more pronounced improvement in the asthmatic condition during this period causing a decrease in compliance. All trial aerosols had the same appearance and the composition of the contents was identical except for the concentration of budesonide. The lowest dose was given by a 25 µl valve and the two other with a 50 µl valve. Budesonide itself has very little, if any, taste. The prescribed dose was two inhalations q.i.d. throughout the study. We are therefore of the opinion that the only possible way to tell the difference between the test drugs is the difference in therapeutic efficacy. PEF values also show the highest dose to be more potent, although this is less evident from the subjective scores.

REFERENCES

1. American College of Chest Physicians and American Thoracic Society: Pulmonary terms and symbols. A report of the ACCP ATS Joint Committee on Pulmonary Nomenclature. *Chest* 67, 583–593, 1975.
2. Björkander, J., Formgren, H., Johansson, S. Å. & Millqvist, E.: Methodological aspects on clinical trials with inhaled corticosteroids: Results of two comparisons between two steroid aerosols in patients with asthma. *Eur. J. Respir. Dis. Suppl.* 122, 63, 108–117, 1982.
3. Brattsand, R., Thalén, A., Roempke, K., Källström, L. & Gruvstad, E.: Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. *Eur. J. Respir. Dis. Suppl.* 122, 63, 62–73, 1982.
4. Ellul-Micallef, R., Hansson, E. & Johansson, S. Å.: Budesonide: A new corticosteroid in bronchial asthma. *Eur. J. Respir. Dis.* 61, 167–173, 1980.
5. Eriksson, N. E., Lindgren, S. & Lindholm, N.: A double-blind comparison of beclomethasone dipropionate aerosol and prednisolone in asthmatic patients. *Postgrad. Med. J.* 51, Suppl 4, 67–70, 1975.

6. Johansson, S. Å., Andersson, K. E., Brattsand, R., Gruvstad, E. & Hedner, P.: Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. *Eur. J. Clin. Pharmacol.* 22, 523-529, 1982.
7. Mygind, N. & Hansen, J.: Beclomethasone dipropionate aerosol effect on the adrenals in normal persons. *Acta Allergol.* 28, 211-218, 1973.
8. Rosenhall, L., Lundqvist, G., Ådelroth, E. & Glennow, C.: Comparison between inhaled and oral corticosteroids in patients with chronic asthma. *Eur. J. Respir. Dis. Suppl.* 122, 63, 154-162, 1982.
9. Toogood, J. H., Baskerville, J. C., Jennings, B., Lefcoe, N. M. & Johansson, S. Å.: Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J. Allergy Clin. Immunol.* 70, 288-298, 1982.
10. Toogood, J. H., Lefcoe, N. H., Haines, D. S. M., et al.: A graded dose assessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. *J. Allergy Clin. Immunol.* 59, 298-308, 1977.
11. Vaz, R., Senior, B., Morris, M. & Binkiewicz, A.: Adrenal effect of beclomethasone inhalation therapy in asthmatic children. *J. Pediatr.* 100, 660-662, 1982.
12. Wyatt, R., Wascheck, J., Weinberger, M. & Sherman, B.: Effect of inhaled beclomethasone dipropionate and alternate day prednisone on pituitary adrenal function in children with chronic asthma. *N. Engl. J. Med.* 299, 1387-1392, 1978.

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