

From the Medical Out-patients' Department, Allergy Clinic
(Head: Egon Bruun, M.D.), Rigshospitalet (University Hospital),
Copenhagen, Denmark.

BECLOMETHASONE DIPROPIONATE AEROSOL (BECOTIDE®) IN SEVERE BRONCHIAL ASTHMA

By

EGON BRUUN & IB HANSEN

It is a long-cherished wish to develop a corticosteroid preparation for local application to the bronchial mucosa in asthmatics in the hope that by exerting its action *in loco* such a drug would be effective in doses lower than needed for oral administration and would thus cause fewer systemic side effects.

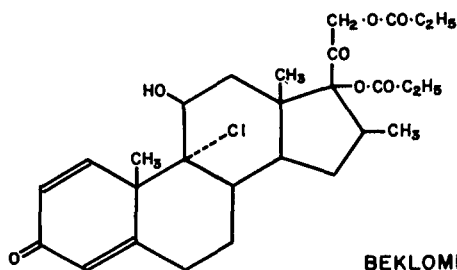
Attempts at establishing steroid spray treatment were made as early as 1951 by Gelfand (8) and have been followed by a number of others (1, 2, 3, 11, 20).

Both hydrocortisone and dexamethasone aerosols have been tried. However, as these have inevitably caused suppression of the adrenal cortex and systemic side effects (13, 15, 17, 19, 22), they have never gained ground.

Beclomethasone dipropionate aerosol (b.d.a.), on the other hand, appears to be effective in bronchial asthma, and in therapeutic doses of 400 μ g daily no action upon the adrenal cortex has been demonstrated (4, 5, 6, 7, 9, 12, 14, 16, 21).

The structural formula of beclomethasone dipropionate is illustrated in Fig. 1. It should be mentioned that it is the dipropionic acid compound which is active. It is rapidly broken down, bacterically int. al., to the less active monopropionate compound.

In 1972 H. Morrow Brown et al. (4) published the clinical results of b.d.a. in the treatment of 60 asthmatics 37 of whom

STRUCTURAL FORMULAE**BEKLOMETASON DIPROPIONAT***Fig. 1.*

Structural formula. Beclomethasone dipropionate.

had been on oral corticosteroid therapy for up to 16 years. Of these 37 patients 28 could be transferred to aerosol only. Somewhat later, also in 1972, S. Lal and associates (12) reported a double-blind trial of the clinical effect of oral prednisone therapy and of b.d.a. aerosol therapy in 38 steroid-dependent asthmatics.

The clinical results were equally favourable by both methods, but the plasma cortisol levels were significantly higher in the aerosol-treated than in the orally treated patients, showing that the aerosol treatment causes less adrenal suppression than the oral treatment.

Our experience of b.d.a. in the treatment of severe bronchial asthma will be presented below. A controlled clinical trial is in progress and will be reported later.

MATERIAL AND METHOD

The study comprises 10 out-patients, aged 30-63 years, with severe steroid-dependent, reversible obstructive bronchial asthma. The maintenance dose of prednisone ranged from 10 to 22½ mg (mean 15 mg) daily and had been continued for years. Periodically all the patients had required higher doses than the continuous minimum dose. Table 1 lists sex, age, duration of disease, and duration of prednisone therapy.

TABLE 1

Patient no.	Age Sex	Duration of asthma (years)	Duration of steroid therapy (years)	Maintenance dose of prednisone in mg daily	
				Before b.d.a.	After b.d.a. for 3 months
1	46 M	7	6	10 (15)	7.5
2	42 F	9	2	10 (20)	5
3	52 M	7	7	20 (30)	7.5
4	48 F	6	4	22.5 (30)	10
5	63 F	6	4	10 (30)	5
6	30 M	10	4	17.5 (60)	12.5
7	50 F	9	5	15 (17.5)	7.5
8	55 F	12	8	17.5 (30)	5
9	52 F	27	17	15 (40)	7.5
10	51 F	13	12	15 (25)	5

Figures in brackets indicate the doses given during exacerbations.

During a period of 3 months, on b.d.a. 400 μ g daily, i.e. two puffs four times daily, the patients' subjective and objective condition was checked. The use of other drugs was recorded daily by the patients. At the out-patients visits peak flow, FEV₁, and vital capacity were measured. Moreover, the patients' continued use of prednisone was adjusted according to the clinical state. Changes, if any, in adrenal suppression were not investigated. Evaluation of these factors is included in another trial in progress in our Clinic and has been reported also in a previous publication (16).

RESULTS

From Table 1 and Fig. 2 it may be seen that in the course of three months' treatment with b.d.a. the oral dose of prednisone could be reduced in all patients—by an average of 50 per cent. Figs. 3, 4, and 5 set out lung function before and after the three months' treatment. Peak flow and FEV₁, in particular, improved, indicating less bronchial obstruction. The patients' average daily consumption of broncholytic sprays dropped from 3.5 to 1.5 puffs daily in the course of the three months. Local side effects were not observed in any case, but

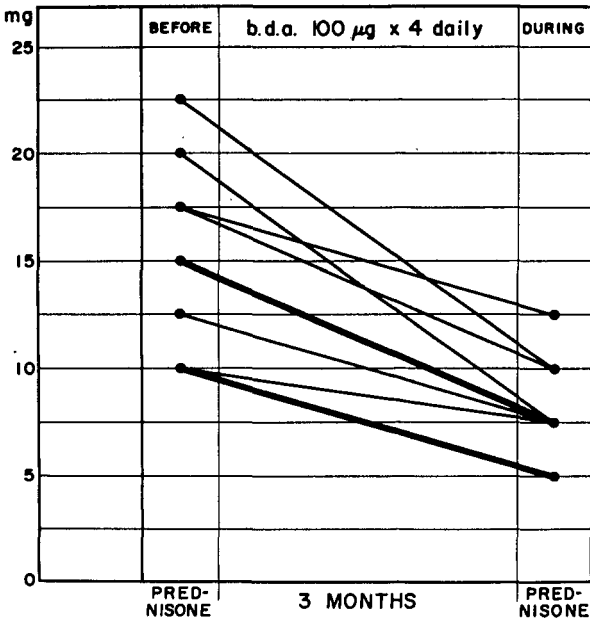


Fig. 2.

Dose of prednisone before and after three months' treatment with beclomethasone dipropionate aerosol (b.d.a.). $p < 0.002$ (Wilcoxon's test).

it must be mentioned that one patient developed broncho-pneumonia during the period of the trial.

Observations in Cases 7 and 9 indicated fewer systemic side effects of b.d.a. than of equipotent doses of prednisone. Case 9 was severely Cushingoid, having several steroid-induced side effects, including spontaneous fractures and cutaneous haemorrhages. In the course of three months' b.d.a. therapy, which rendered it possible to reduce prednisone from 15 mg to $7\frac{1}{2}$ mg daily, the Cushingoid appearance decreased, and the cutaneous haemorrhages disappeared. In Case 7 there was an excellent response of the asthma to b.d.a., but when the dose of prednisone had been reduced by half she developed severe attacks of vasomotor rhinitis which had presumably so far been kept in check by the systemic effect of prednisone.

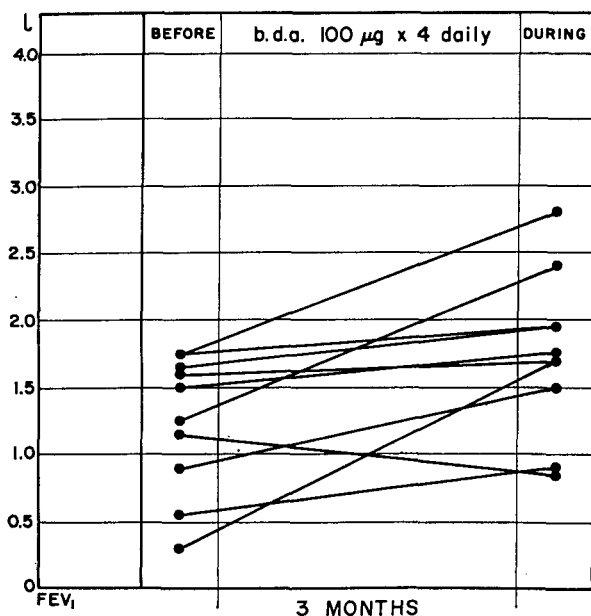


Fig. 3.

FEV₁ before and after three months' treatment with beclomethasone dipropionate aerosol (b.d.a.). $p < 0.03$ (Wilcoxon's test).

DISCUSSION

The effect of b.d.a. upon bronchial asthma substantiated in previous publications was confirmed in the present, open study. Even though the material was selected with a view to severe long-standing bronchial asthma requiring relatively high doses of steroid, the mean dose of prednisone could be reduced by 50 per cent. At the same time, the use of broncholytics dropped to less than one-half, and improvement in lung function was recorded by FEV₁ and peak flow. In therapeutic effect the dose of b.d.a., 400 µg daily, was equivalent to 7–8 mg prednisone which represents the mean reduction of orally administered prednisone. According to several authors this dose of b.d.a. has no or only negligible systemic effects.

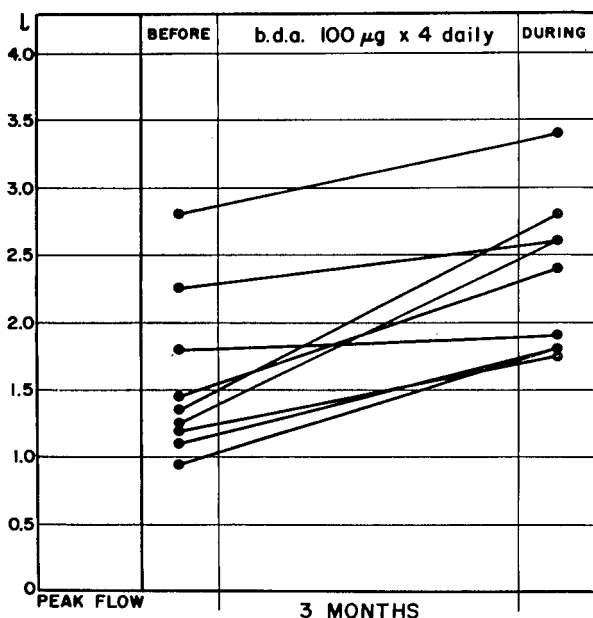


Fig. 4.

Peak flow values before and after three months' treatment with beclomethasone dipropionate aerosol (b.d.a.). $p < 0.004$ (Wilcoxon's test).

That b.d.a. acts predominantly *in loco* on the bronchial mucosa is supported by the unmasking of other allergic symptoms as observed in Case 7 after reduction of the oral dose of prednisone. Such observations have been reported also by others (4). Our finding, that b.d.a. can really achieve something also in severe, long-standing cases, has recently been demonstrated also by Maberly et al. (14) who obtained results largely on a level with our. Their investigation also showed a definite increase in the plasma cortisol levels when the patients were transferred to b.d.a. which made it possible to reduce the dose of prednisone.

Let it be pointed out that in acute, severe exacerbations of asthma with bronchospasm the patients often still require prednisone, orally and/or parenterally. In such situations, the

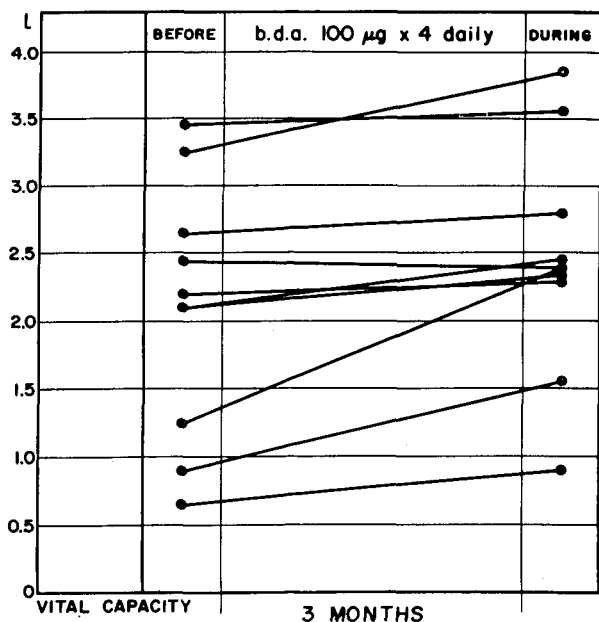


Fig. 5.

Vital capacity before and after three months' treatment with beclomethasone dipropionate aerosol (b.d.a.). $p < 0.004$ (Wilcoxon's test).

efficacy of b.d.a. may be reduced—a fact well-known from the use of other inhalation drugs in bronchial asthma.

Local long-term side effects, if any, in the form of an increased tendency to infections and a degeneration of the elastic tissue in the respiratory tract, have not yet been definitely elucidated, but in theory they may be feared. It is well-known that long-lasting use of potent steroid ointments may entail destruction of the elastic tissues of the skin (18). However, these two modes of application are not directly comparable, as b.d.a. is presumably rapidly absorbed, whereas the ointment base of most ointments endeavours to keep the steroid content for as long as possible in the cutaneous tissues. Moreover, it may be mentioned that histopathological studies of the respiratory mucosa from dogs which received b.d.a. through one year did not show any abnormalities (10).

Fig. 6.

The patients' drug consumption before/after 3 months' treatment with becotide.

Age Sex	Ventolin Alupent spray	Imurel tabl. mg	Lomudal caps.	Bisolvon tabl.	Novatro- fedrin tabl.	Theofylla- min tabl.
1. 46 M	10/6		4/2			
2. 42 F	3/0		3/0			6/6
3. 52 M	4/0					8/0
4. 48 F	5/3					
5. 63 F	4/0				3/0	3/1
6. 30 M	2/2		4/0			6/3
7. 50 F	2/4			6/0		6/6
8. 55 F	4/0	150/100				6/6
9. 52 F			4/0			
10. 51 F			2/0			6/6

SUMMARY

In a selected material of 10 patients with severe, steroid-dependent bronchial asthma the oral dose of prednisone could be reduced by an average of 50 per cent in an open trial of beclomethasone dipropionate aerosol (b.d.a.) 400 µg daily for 3 months. At the same time, the use of broncholytics dropped to less than one-half, and an improvement of lung function was recorded.

Biochemical studies for assessing suppression were not performed in the present study, but the clinical findings in two cases indicated fewer systemic side effects of b.d.a. than of equipotent doses of prednisone.

The possibility of local long-term side effects is pointed out. What might be feared, in particular, is an increased tendency to infections in the respiratory tract and a risk of degeneration of the elastic tissues in the pulmonary mucous membranes.

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