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BECLOMETHASONE DIPROPIONATE AEROSOL IN LONG-TERM TREATMENT OF PERENNIAL AND SEASONAL ASTHMA IN CHILDREN AND ADULTS: A REPORT OF FIVE-AND-HALF YEARS' EXPERIENCE IN 600 ASTHMATIC PATIENTS

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1 Clinical experience in the long-term treatment of allergic asthma with beclomethasone dipropionate aerosol (BDA) during the past five-and-half years is reviewed. A total of 600 patients from National Health Service and private practice, including 176 children, was treated.

2 A total of 241 patients, including 57 children, was corticosteroid-dependent for 1–18 yr. Of these patients, 70% were successfully transferred to BDA, 21% could be only partially transferred, and 9% could not. Over the years, 12% had to revert to oral corticosteroids, but 4% were able to stop BDA without relapse. Oropharyngeal thrush was observed in 16%, but in only two cases did treatment have to be withdrawn on that account. There were no deaths from asthma, and seven normal births.

3 A total of 359 non-corticosteroid-dependent asthmatics, including 119 children, were also treated with BDA. Successful control of symptoms was achieved in 99%, but 4% eventually became corticosteroid-dependent. There were three deaths from asthma and 13 normal births. Fifteen per cent were able to stop treatment without relapse. Five per cent developed oropharyngeal candidiasis, but treatment did not have to be stopped on that account.

4 In 35% of both groups, a preliminary course of oral corticosteroid at high dosage was required before the introduction of BDA therapy. Sixty-two patients were treated for over 5 yr, and approximately 1350 patient-years of BDA have been given without evidence of side-effects.

5 Thirty-one corticosteroid-dependent and 73 non-corticosteroid dependent patients with perennial asthma had 231 seasonal episodes, effectively controlled in 68%, and 38 purely seasonal asthmatics had 100 episodes, with good control in 80% of cases.

Introduction

Since our first clinical trial was published (Brown *et al.*, 1972), many other investigators have confirmed that beclomethasone dipropionate aerosol (BDA) is effective in the control of asthma. We have confirmed our original findings in children with seasonal asthma and hay fever, and have reported our long-term experience in the treatment of perennial and seasonal asthma, and also allergic rhinitis (Brown & Storey, 1973, 1974, 1975; Brown *et al.*, 1977). The place of any new remedy in therapeutics can be established only after long experience, and the purpose of this report is to review our results for the five-and-half year period from June 1970 to December 1975.

Case selection and methods

The indications for treatment with BDA have not altered since the first clinical trial, excess of eosinophil cells in the sputum or nasal smears being demonstrable in all cases (Brown, 1958). Intensive investigation of allergic factors, using methods described previously, was undertaken in every case (Brown, 1970). Objective data on the severity and diurnal patterns of airways obstruction and response to treatment were obtained by issuing peak flow meters (PFM) for individual use. The minimum pretreatment control period on PFM monitoring was 2 weeks, but many patients were monitored before treatment for months or even years. All patients had been suffering

from asthma for at least one year.

Dosage and administration of BDA

BDA was administered by metered aerosol (50 μg per 'puff'). After preliminary complete expiration, the aerosol was discharged simultaneously with a sudden deep inspiration. This is essential to ensure that BDA reaches the bronchi. Personal instruction was given in the use of the aerosol, and the patient's technique was checked at several visits until satisfactory. The patients were told that BDA does not act immediately, that it must be taken on a regular daily basis, and that reduction in dosage must be made gradually. Many patients had already had a trial of the treatment on the advice of their general practitioners, but few of them had benefitted from it because of incorrect usage of the aerosol or inadequate dosage. Placebo aerosols are useful for demonstration purposes, since many patients use bronchodilator aerosols incorrectly. A salbutamol aerosol used shortly before the inhalation of BDA helps to ensure that the corticosteroid aerosol reaches the bronchi.

It must be emphasized that if a patient is short of breath, he will have difficulty in achieving effective inhalation of an aerosol. When airways obstruction is severe, BDA may cause bronchial irritation, and the asthma may become worse. In this situation it is necessary to relieve the airways obstruction by an adequate course of oral corticosteroids in high dosage before introducing BDA. Doses of prednisolone of up to 40 mg daily for a week or more are frequently necessary in these circumstances.

In the past 3 yr we have found that the most practical dosage of BDA is three metered doses three times daily. Initially, we used two doses four times daily, but the mid-day dose was often forgotten, or was inconvenient to take at school or at work. In children, and in adults where there is a difficulty in usage, it is advisable to prescribe three metered doses four times daily initially, since very little may reach the bronchi until the correct technique is used.

Corticosteroid-dependent group (241 cases)

This group comprised 229 asthmatics who had been corticosteroid-dependent for 1–18 yr, and 12 who had been given corticotrophin for 1–5 yr. Many attempts to withdraw corticosteroids had been unsuccessful, the degree of airways obstruction varied widely, and the age range was from 2.5–68 yr. Daily dosages were 0.5–1.5 mg betamethasone phosphate (Betnesol), a soluble corticosteroid unlikely to produce gastric side-effects (Brown, 1961).

Method of transfer

Transfer from oral to aerosol corticosteroids was effected by adding BDA to the regimen, and gradually phasing out oral treatment. In our initial studies (Brown *et al.*, 1972) corticosteroids were withdrawn too quickly. Our present practice is to transfer the patients to 1-mg prednisolone tablets, equivalent to their usual total daily maintenance dose, and then to reduce the dose by 1 mg daily with regular PFM monitoring. Much slower withdrawal is necessary when corticosteroids have been used for a long period, the speed of withdrawal being a matter of clinical judgment. An obvious recurrence of symptoms was seldom observed until the maintenance dose of prednisolone was down to 3 mg daily.

All ex-corticosteroid-dependent patients were given a personal supply of prednisolone for emergency use, with clear instructions on the dosage to be taken in the event of an asthmatic attack. A yellow warning label was affixed to their 'steroid cards' regarding suppression of adrenal function for up to 2 yr.

Table 1 Results in 229 corticosteroid-dependent and 12 corticotrophin-dependent cases (31 also seasonal)

Age commenced treatment with BDA (yr)	*2–14*		*15–29*		*30–44*		*45–59*		*60+*		*Overall result*	
	Number	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Total completely transferred	51	90	18	64	47	73	38	59	13	48	167	70
Increase in average PEF	23	40	0	0	18	28	13	20	2	7	56	24
100%+	19	34	6	21	16	25	9	14	7	26	57	24
50–100%												
0–50%	9	16	12	43	13	20	16	25	4	15	54	22
Partial transfers	3	5	9	32	12	19	19	29	9	33	52	21
Failed transfers	3	5	1	4	5	8	8	12	5	19	22	9
Totals	57		28		64		65		27		241	
Late failures	3	5	3	12	9	14	13	20	1	4	29	12

Results

Table 1 shows that the best results were obtained in the younger age groups. The large number of patients in whom the peak expiratory flow (PEF) was more than doubled suggests that the maintenance dose of oral corticosteroids in these cases may have been inadequate for full control, although the optimum dose would undoubtedly have produced unacceptable side-effects.

Oral corticosteroids were withdrawn in 70%, and the failure rate was only 9%. In the remaining 21%, the dose of oral corticosteroid was reduced, indicating that BDA had a corticosteroid-sparing effect. Dosage in this group varied from 3–5 mg prednisolone daily. The data show that the degree of reversibility decreases, and the incidence of failure and partial transfer increases, with advancing years. Even those in the older age groups, who could be only partially transferred to BDA were, however, much better controlled. Partial transfers became more common as larger numbers joined the group. Late failures are a new category, where control by BDA alone was eventually lost in 12% and a return to oral corticosteroids was unavoidable.

Relief of side-effects and complications on transfer Table 2 summarizes these aspects of transfer, the most obvious beneficial effect being loss of Cushingoid features. Atrophic changes in the skin were slow to recover, and were never complete, but the tendency to bruise often became less marked within a month of transfer. Improvement in osteoporotic changes in the vertebrae could be assessed only by the disappearance of back pain. Reduced insulin requirements in two cases with concomitant diabetes have already been reported (Brown & Storey, 1973), but the child whose diabetes was unmasked only when he had to be given high doses of oral corticosteroid has now become an established diabetic.

Withdrawal rhinitis, eczema and nasal polypi caused problems in 65 patients. Oral corticosteroid therapy must have suppressed these allergic phenomena, which were unmasked on transfer to BDA. Long-term results of BDA therapy in nasal allergy are being reported separately (Brown & Storey, 1977).

Table 2 BDA in treatment of corticosteroid-dependent asthma, relief of side-effects and complications of transfer in 241 cases

Regression of moon face and loss of weight	85
Diabetes mellitus: reduced insulin requirements	2
Steroid-induced dyspepsia	15
Osteoporosis	10
Unmasking of allergic rhinitis	37
Exacerbation of eczema	20
Tiredness, lassitude, and aches and pains	80
Recurrence of polypi	8
Regression of skin atrophy and bruising	24

Eighty patients experienced obvious corticosteroid withdrawal symptoms lasting for various periods, being most severe after many years of treatment. Two patients refused to endure such symptoms, preferring to continue on oral corticosteroids, and 52 of the whole group of 241 became partial transfer cases, remaining well controlled on prednisolone 3–4 mg daily plus BDA.

Corticotrophin seemed ineffective in alleviating withdrawal symptoms, although perhaps it was not continued for a sufficiently long period, as suggested by Hugh-Jones *et al.* (1975). Tetracosactrin zinc produced acute hypokalaemia in two patients, possibly because of the differential effect of stimulating an intact and functioning zona glomerulosa and an atrophic zona fasciculata of the adrenal glands. Encouragement and reassurance that patience would have its reward seemed the best approach. All these effects have been noted in previous publications, and have become familiar to all who have been involved in using this treatment in corticosteroid-dependent asthmatics.

Long-term dosage levels and value of clinical allergy techniques Table 3 summarizes maintenance dosage levels of BDA required after transfer. A few patients required larger doses of 600 µg daily, the usual dose being 450 µg daily. In 29% a smaller dose proved adequate.

As shown in Table 6, 80 (33%) patients in this group had been taking BDA for over 3 yr, 131 (54%) for over 2 yr and 169 (74%) for over 1 yr. Twelve patients were able to stop treatment without relapse, but 20 have been lost to follow-up. Twenty-five of the original series have now been maintained on BDA for over 5 yr, without loss of control except for an occasional exacerbation requiring a short course of oral corticosteroid. The incidence of infection has not been higher than before BDA therapy, and in some cases it has been lower.

At this Centre, intensive allergy studies are carried out on all patients, but specific hyposensitization is undertaken only if objective proof is indicated by nasal provocation tests (Brown, 1970). It would have been unethical to withhold such treatment in long-term patients, and the use of hyposensitization made possible the transfer to BDA of 51 (21%) patients in this group. Thus, the failure rate without hyposensitization would have been 30% in this group of corticosteroid-dependent patients. A further six patients were able to stop all treatment because of avoidance of known allergens or hyposensitization, whereas another six stopped treatment without relapse for no ascertainable reason.

Oropharyngeal candidiasis The incidence of

oropharyngeal candidiasis is noted in Table 3, where it is clear that this problem, along with hoarseness, is much more common in corticosteroid-dependent patients. There was no doubt that this side-effect was dose-dependent, and usually responded rapidly to amphotericin B lozenges; but in two cases BDA had to be withdrawn. Evidence of infection was not sought routinely, nor were routine mycological investigations carried out, as in the studies of McAllen *et al.* (1974), Brompton Hospital/MRC Collaborative Trial (1974) and Milne *et al.* (1974). Patients are now instructed to drink or gargle immediately after inhaling BDA to prevent the aerosol from being deposited on the pharyngeal mucosa. Hoarseness was troublesome in some cases, but laryngoscopy disclosed no evidence of *Candida albicans* infection of the larynx.

Miscellaneous aspects Table 4 illustrates that in 37% of patients the airways obstruction was so severe as to require initial treatment with oral corticosteroids in high dosage. The dose was then tapered off, and BDA introduced when the dose of prednisolone was down to 15 mg daily. At this stage, the airways obstruction had usually been substantially relieved, and the patient had no difficulty in inhaling the aerosol.

Out of 57 corticosteroid-dependent children 34 (60%) began to regain the growth they had lost while on oral corticosteroid therapy. In this group seven normal babies have been born. No patient died from asthma, two died from myocardial infarction and two from other causes.

Table 3 BDA in treatment of asthma

Maintenance dosage level and other data	*241 Corticosteroid-dependent cases*	*%*	*359 Non-corticosteroid-dependent cases*	*%*
600 µg	36	15	25	7
450 µg	115	48	173	48
300 µg	35	15	85	24
200 µg or less	33	14	71	20
Difficulty in transfer or in stabilization before hyposensitization	51	21	52	14
Stopped without relapse without hyposensitization	6	2	35	10
Stopped without relapse because of hyposensitization or avoidance	6	2	19	5
Candida albicans infection once or more	38	16	17	5
Hoarseness	16	7	5	1

Table 4 BDA in treatment of asthma (miscellaneous data)

		241 Corticosteroid-dependent cases		*359 Non-corticosteroid-dependent cases*	
		Number	*%*	*Number*	*%*
Initial high dose oral corticosteroids necessary		89	37	122	33
Growth restarted		34	14	12	3
Sodium cromoglycate	Effective	28	12	45	13
	Ineffective	146	60	139	39
	Not tried	67	28	170	47
Aspergillosis effectively treated		7	3	6	2
Aspergillosis not effectively treated		9	4	0	0
Died of asthma		0	0	3	1
Died of cardiac causes		2	1	3	1
Died of other causes		2	1	0	0
Normal babies delivered		7	3	13	3

Causes of failure to transfer to BDA Table 5 shows that infection and hypersecretion, which must prevent the aerosol from penetrating to the bronchial mucosa, are the most common causes of failure, partial failure or late failure to transfer from oral to aerosol therapy. The irreversible allergic group had sputum containing abundant eosinophils, but no improvement in airways obstruction was obtained either with large doses of oral corticosteroid or with BDA. A few cases admitted to the study in error without sputum examination were later found unresponsive, and were shown to have typical bronchitic sputum cytology, with excessive numbers of macrophages but no eosinophils (Brown, 1958).

Table 7 compares the results of BDA in 'extrinsic' and 'intrinsic' types of asthma. A better response was usually obtained in the 'extrinsic' group.

Allergic bronchopulmonary aspergillosis In 22 cases of allergic bronchopulmonary aspergillosis,

Table 5 BDA in treatment of allergic asthma (causes of failure)

	Corticosteroid-dependent			*Non-corticosteroid-dependent*	
	Initial failure	*Partial transfer*	*Late failure*	*Initial failure*	*Late failure*
Frequent infection and hypersecretion	4	24	16	3	6
Persistent thrush	2	—	—		—
Irreversible allergic	9	28	11	2	8
Not allergic	3	—	—	—	—
Passed from allergic to bronchitic phase	—	—	2	—	—
Irritation in use	2	—	—	—	—
Totals	20	52	29	5	14

Table 6 BDA in treatment of perennial asthma (duration of treatment to 31 December, 1975)

	241 Corticosteroid-dependent cases		*359 Non-corticosteroid-dependent cases*	
Duration of treatment	*Number*	*%*	*Number*	*%*
5–5.5 yr	25	10	37	10
4–5 yr	22	9	76	21
3–4 yr	33	14	77	21
2–3 yr	51	21	61	17
1–2 yr	38	16	23	6
6–12 months	40	17	6	2
Stopped without relapse	12	5	54	15
Lost to long-term follow-up, presumably still on treatment	20	8	25	8

Table 7 BDA in treatment of asthma (comparison of results in extrinsic and intrinsic classes)

	241 Corticosteroid-dependent				*359 Non-corticosteroid-dependent*			
	Intrinsic	*%*	*Extrinsic*	*%*	*Intrinsic*	*%*	*Extrinsic*	*%*
Over 100% increase in PEF	19	18	37	27	40	40	85	33
50–100% increase in PEF	17	17	40	29	33	33	105	41
0–50% increase in PEF	24	23	30	22	27	27	64	25
Partial transfer	30	29	22	16	–	–	–	–
Complete failure	13	13	9	1	1	1	4	1
Totals	103		138		101		258	

good results were obtained (Table 4) without any overgrowth of fungus in the sputum. Only three of this group were excreting *Aspergillus fumigatus* in sputum, but all had at one time the appropriate X-ray findings, and Type 3 skin reactions. Not all had precipitins in the serum, and our experience was similar to a previous report (Hilton & Chatterjee, 1975), using the same diagnostic criteria.

Non-corticosteroid-dependent group (359 cases)

Table 8 summarizes the overall results, by age groups and by degree of reversibility. In many cases the degree of airways obstruction was more severe than in the corticosteroid-dependent patients. In 33% oral corticosteroids in high dosage were required to relieve the airways obstruction before introduction of BDA.

The results were better than in the corticosteroid-dependent group, with fewer failures and a greater degree of reversibility in the older age groups. Late failure after initial success in 14 cases was again a feature which has gradually become more apparent with long-term experience.

Dosage requirements (Table 3) were lower in this group, 43% requiring less than 450 μg daily. Thirty-five patients (10%) were able to stop treatment without relapse, and another 19 (5%) after hyposensitization or avoidance of allergens. As in the corticosteroid-dependent group, there was difficulty in obtaining adequate control in 52 cases (14%) until hyposensitization was undertaken.

Oropharyngeal candidiasis (Table 3) was a lesser problem, possibly because of the smaller doses, and hoarseness was less frequent. Twelve children (10% of this group) had growth retardation, presumably as an effect of chronic asthma, because their growth rate increased after the introduction of BDA. There were three deaths from asthma in this group, as compared with none in the corticosteroid-dependent group.

Failure (Table 5) was usually associated with hypersecretion and frequent bronchial infection, and with irreversible allergic airways obstruction. Late failure after initial success was again a feature.

As shown in Table 6, 190 (53%) of this group had been treated for over 3 yr, 251 (70%) for over 2 yr, and 274 (76%) for over 1 yr. Fifty-four (15%) were able to stop treatment without relapse, three times the proportion in the corticosteroid-dependent cases.

Table 8 Results in 359 non-corticosteroid-dependent asthmatics (including 73 with seasonal factors)

Age commended treatment with BDA (yr)	*2–14*		*15–29*		*30–44*		*45–59*		*60+*		*Overall result*	
	Number	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Total established BDA	119	100	44	96	90	97	79	100	25	100	354	99
Increase in average PEF												
100%+	43	36	18	39	26	29	31	39	7	28	125	35
50–100%	53	45	14	30	36	40	25	32	10	40	138	38
0–50%	23	19	12	27	25	28	23	29	8	32	91	26
Failed to establish	0	0	2	4	3	3	0	0	0	0	5	1
Totals	119		46		90		79		25		359	
Late failures	2	2	1	2	7	8	3	4	1	4	14	4

Seasonal asthma

The results for 331 seasons in 142 patients are summarized in Table 9, which includes 38 purely seasonal cases who were not otherwise included in this report. Care was taken to ensure that no other treatment, except bronchodilators, was used, so as to

assess the value of BDA alone. This summary is an extension of our previous report (Brown & Storey, 1974). The pollen and spore counts are monitored daily at this Centre, so that peaks of allergen challenge are known and can be correlated with the PEF recordings. The counts obtained in Derby are consistently much higher than those reported in London, often by a factor of three or even four.

Perennial asthma, well controlled by BDA in winter, can be seriously affected by seasonal factors in very sensitive cases. Specific hyposensitization may be required to diminish or abolish seasonal exacerbations. In purely seasonal cases, results are much better, but abrupt falls in PEF and exacerbations of symptoms often coincide with peaks of the pollen or mould spore counts.

Pregnancy and BDA

Twenty of our 600 patients became pregnant, and were delivered of normal children. There were no abortions, spontaneous or therapeutic.

Discussion

This report, involving the treatment of 600 patients with BDA, 241 previously corticosteroid-dependent, for up to five-and-half years, is reassuring in that no new side-effects have appeared in a total of approximately 1350 patient-years of treatment. Oropharyngeal candidiasis has not been a significant problem in this series, but was commoner in the corticosteroid-dependent group. The incidence is similar to that in other reports, with one notable exception. McAllen *et al.* (1974) reported a 13% incidence of *C. albicans* infection of the pharynx, larynx or both. Milne & Crompton (1974) found yeasts in 41% of throat swab cultures, but clinical thrush in only 5.5%, and the Preliminary Report of the Brompton Hospital/MRC Collaborative Trial (1974) reported a dose-dependent cumulative increase in clinical thrush increasing to 45% at 28 weeks in patients on 400 μg daily, and 77% at 800 μg daily; but the thrush was never severe enough to necessitate stopping treatment. It is difficult to assess the true significance of these reports, or of the contentious correspondence (Grant *et al.*, 1974) which followed the last publication, but from the clinical point of view there has fortunately been no problem of any significance in our series. Our impression is that a drink or a simple gargle after the inhalation of BDA, and improved dental hygiene, has resulted in fewer cases of clinical thrush in recent years.

The major problems were all concerned with corticosteroid withdrawal symptoms and unmasking of other allergic manifestations. The policy of providing each patient, or the parents of children, with an emergency supply of corticosteroid for immediate use without medical advice has undoubtedly proved of value in the corticosteroid-dependent group. Disaster might otherwise have occured, as in three of the five sudden asthma deaths recently reported from Australia by Mellis & Phelan (1977). Their detailed case reports suggest that the timely administration of an effective dose of corticosteroids might have averted the fatal outcome in some of these cases, that normal tetracosactrin tests can be deceptive, and that occasional sophisticated pulmonary function tests may be inferior to frequent PEF recordings, which provide an early warning system. Continuity of care and immediate access to a chest physician when problems arise are other factors which we believe are vital to success. It is notable that all asthma deaths occurred in the non-corticosteroid-dependent group, illustrating the unpredictable nature of the disease and its constant dangers.

The availability of large numbers of PFMs is considered essential for accurate monitoring. Many patients are quite unaware of the severity of their airways obstruction until it is monitored in this

Table 9 BDA in treatment of seasonal asthma (results in 142 cases for seasonal aspects only)

	Total cases	*Total seasons*	*Good control*		*Poor control*	
			Number	*%*	*Number*	*%*
From corticosteroid-dependent group	31	88	58	66	30	34
From non-corticosteroid-dependent group	73	143	99	69	44	31
From purely seasonal group	38	100	81	81	19	19
Totals	142	331	238	72	93	28

All cases had positive nasal challenges before season and had no desensitization therapy.
Good control means no asthma, or transitory breakthrough only.
Poor control means repeated attacks requiring other therapy.

way. Relief of airways obstruction by means of a course of oral corticosteroid at high dosage before the introduction of BDA is a technique which has undoubtedly contributed greatly to successful treatment.

Our long experience with BDA, allied with similarly encouraging reports from most countries in the world, indicates that the efficacy of this treatment in asthma has now been fully established, and offers hope of independence from oral corticosteroid therapy and its side-effects to many thousands of asthmatics. Our data suggest that the effectiveness of BDA is in proportion to the degree of reversibility of the airways obstruction, and whether the bronchi can be rendered sufficiently patent for the aerosol to be effectively inhaled.

Although BDA is clearly an important advance in treatment for the corticosteroid-dependent asthmatic, its place in the treatment of milder cases is less clear. It is generally assumed that bronchodilators and sodium cromoglycate should be tried first, and that BDA should be introduced only if these drugs are ineffective. In the light of our own experience, however, it seems justifiable to suggest that in cases of chronic asthma of moderate severity BDA should be used as soon as it is apparent that bronchodilator requirements are increasing.

The absence of long-term side-effects and the reversal of airways obstruction usually obtained with BDA suggests that it is now the treatment of choice for asthma of moderate severity, particularly in younger patients who have a greater chance of spontaneous recovery.

It must be emphasized that, with the exception of patients who are able to stop treatment with BDA without relapse, this method of treatment is still only a means of suppressing the allergic reaction without disturbing pituitary–adrenal function (Harris *et al.*, 1973; Buisseret, 1973; Maberly *et al.*, 1973). Although its proper use may enable many patients to lead a normal life for the first time in many years, such results should not obscure the fact that the cause or causes of the asthma are still present and often unidentified. The long-term results presented here would have been less satisfactory without the use of specialized diagnostic methods and hyposensitization.

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