EXPERIENCE WITH THE USE OF A CORTICOSTEROID AEROSOL

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- 1 In 48 patients with chronic asthma who had been receiving treatment with beclomethasone dipropionate aerosol (BDA) at a daily dose of 400 µg for several years, observations were made on the effect of increasing the dose to 800 µg daily for 6 months.
- 2 There was subjective improvement in 37 of the 48 patients, but the only objective evidence of improvement was a slight reduction in airways resistance.
- 3 The higher dose of BDA did not produce impairment of pituitary–adrenal function or an increase in the incidence of oropharyngeal candidiasis.

Introduction

Much has already been written about the beneficial action of beclomethasone dipropionate aerosol (BDA) in controlling asthma (Brown *et al.*, 1972; Lal *et al.*, 1972; Chatterjee *et al.*, 1972; British Thoracic and Tuberculosis Association Multicentre Trial, 1976). At the usual therapeutic dose of 400 µg–600 µg daily, good control of the symptoms of asthma has been achieved, with no evidence of adrenal suppression. Indeed, Maberly *et al.* (1973) have demonstrated that there are signs of recovery of adrenal function when the aerosol is used in place of oral corticosteroids in those patients whose adrenal function was previously impaired. Oropharyngeal candidiasis has been the only side-effect reported (Brompton Hospital/Medical Research Council Collaborative Trial, 1974), but this is seldom sufficiently troublesome to cause the treatment to be withdrawn.

This study is an evaluation of patients who had taken BDA 400 µg daily for several years, followed by 800 µg daily for 6 months. It was designed to answer the following questions: (1) Was there any improvement in respiratory function on doubling the dose of BDA? (2) Did the higher dose have any

suppressing effect on the hypothalamo–pituitary–adrenal (HPA) axis, using the short tetra-cosactrin (Synacthen) test to measure adrenal function? (3) Was the incidence of clinical thrush increased when the dose was doubled? (4) Were any other adverse biochemical changes caused by the higher dose of BDA?

Methods

Patients diagnosed as suffering from ‘bronchial asthma’ or ‘reversible airways disease’ were included in the study. Most of them had required short courses of oral corticosteroids during acute episodes, but no patient was taking this treatment continuously. The series consisted of 48 patients, aged 11–71 yr (mean 50 yr). The duration of the illness varied from 9 months to 52 yr (mean 13.9 yr). Of the 48 patients in the study, 30 were diagnosed as suffering from bronchial asthma with no other disease. Of the remaining 18 patients, five were additionally diagnosed as suffering from bronchitis, five from emphysema, five from bronchitis and emphysema and one from bronchitis and angina, one from hay fever and one from bronchiectasis. The degree of severity of the asthma, when BDA was first prescribed, was classified as very severe, severe or moderate. These were subjective evaluations by one clinician. Table 1 shows the status of the patients when the drug was first prescribed.

Table 2 shows the response of the 48 patients to treatment with BDA 400 µg daily immediately before the dose was increased to 800 µg daily. All the patients were then observed for a period of 6 months

Table 1 Severity of asthma in 48 patients when BDA was first prescribed

Asthma	Very severe	Severe	Moderate
Worsening	10	20	15
Stable	0	1	1
Improving	0	1	0
Total	10	22	16

on the higher dose. Routine respiratory function tests were carried out on every patient at each visit. These included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF) and airways resistance (RAW). Objective assessment of HPA function by tetracosactrin challenge (Greig *et al.*, 1969), was made before and after 3 and 6 months' treatment with BDA 800 μ g daily. If any patient was taking additional treatment for asthma, this was continued unchanged. Every patient was instructed to rinse out the mouth with tapwater after each aerosol inhalation.

Dentures, where used, were cleaned thoroughly every day. None of the female patients was on oral contraceptives. The mouth and throat were inspected at each visit, and a throat swab was examined for *Candida albicans*, when the patients were receiving BDA 400 μ g daily, and again when the dose was increased to 800 μ g daily. Blood was taken for haematological and biochemical examination before the dose was increased to 800 μ g daily, and at 3 and 6 months thereafter.

Results

Before entering the study at the 'low dose' level (that is, BDA 400 μ g daily), every patient was being treated with bronchodilator drugs. It was decided, wherever possible, to standardize such treatment by using either inhaled or oral salbutamol. During the 'high dose' phase of the study (that is, BDA 800 μ g daily), 27% of patients took salbutamol only occasionally, and one patient required no bronchodilator preparation at all.

Forty-four of the 48 patients were, before the start of the study, taking sodium cromoglycate three times daily but by the end of the study all but one patient found that they no longer required that form of treatment.

Table 3 shows the response, after a period of 6 months, of the 48 patients to an increase in the dose of BDA from 400 μ g to 800 μ g daily. Measurements of FEV_1 , FVC, PEF and RAW were carried out immediately before the daily dose of BDA was increased to 800 μ g, and after the patient had been taking this dose for 3 months and for 6 months. The results are shown in Table 4.

It can be seen that the less sensitive methods of measuring pulmonary function (FEV_1 , FVC and PEF) showed no change in respiratory function on doubling the dose of BDA, but a slight improvement was recorded at 6 months by measurement of RAW, using a body plethysmograph. Subjectively, the patients reported feeling better, and from a clinical point of view they seemed to have improved. At the higher dose no suppression of adrenal function was detected even after 6 months, the mean plasma cortisol level then being 300 nmol/l. Five patients had positive throat swab cultures for *Candida albicans* when treated with BDA 400 μ g daily. In every case the symptoms responded to treatment with amphotericin lozenges or to simple mouthwashes. Only three patients developed clinical thrush while taking the higher dose. One of these also had thrush while on the lower dose. This is in contrast to the findings of Costello & Clark (1974), who noted an increase in clinical thrush as the dose of beclomethasone dipropionate was increased. No other biochemical changes were detected in any patient after 6 months' treatment on the higher dose.

Table 2 Effect of treatment with BDA 400 μ g daily in 48 patients

Effect of treatment	Number of patients
Marked improvement	19
Definite improvement	15
Marginal improvement	10
No change	4
Worse	0
Total	48

Table 3 Effect of treatment with BDA 800 μ g daily in 48 patients

Effect of treatment	Number of patients
Marked improvement	20
Definite improvement	17
Marginal improvement	11
No change	0
Worse	0
Total	48

Table 4 Respiratory function in patients receiving BDA 800 μ g daily

Measurement	Number of patients	Mean value at 0 months	Mean value after 3 months	Mean value after 6 months
FEV_1 (l)	48	1.84	1.88	1.82
FVC (l)	48	3.33	3.30	3.30
RAW (cm/l/s)	32	6.00	6.20	4.89
PEF (l/min)	31	251.80	254.60	267.30

Discussion

Gaddie *et al.* (1973) failed to demonstrate any improvement in respiratory function on increasing the dose of beclomethasone dipropionate in 15 patients. The likeliest explanation for this finding is that these patients had already achieved their maximum increase in respiratory function at the lowest dose used (400 µg daily). In contrast, Costello & Clark (1974) demonstrated an improvement in FEV₁ in five patients on doubling the dose, and similar findings were recorded in the Brompton Hospital/Medical Research Council Collaborative Trial (1974). Adrenal function was tested in these three studies, and no significant impairment of adrenal function was detected on increasing the dose to 800 µg daily. Although Gaddie *et al.* (1973) noted a smaller incremental increase in the response to a tetracosactrin challenge at 1600 µg daily, the test was well within the defined normal limits (Greig *et al.*, 1969).

The findings reported in this study are broadly in agreement with those of other workers. Objective improvement in respiratory function was shown only by whole-body plethysmography. No adrenal suppression was observed at a dose of 800 µg daily even after 6 months' treatment. It is perhaps surprising that there was no increased incidence of oral thrush, which most other workers have reported following an increased dose of BDA. We can offer no explanation for this finding.

In those patients whose symptoms were inadequately controlled by BDA 400 µg daily an increase in the dose to 800 µg daily may be followed by an improvement in symptoms and respiratory function, with little risk of adrenal suppression. Oropharyngeal thrush may be an increased hazard under these circumstances, but this condition usually responds to local antifungal treatment, without the need to discontinue therapy. We would therefore advocate the higher dose whenever it is indicated.

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