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Response of patients receiving high dose beclomethasone dipropionate

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Costello, J. F. and Clark, T. J. H. (1974). *Thorax*, **29**, 571–573. **Response of patients receiving high dose beclomethasone dipropionate.** Beclomethasone dipropionate was inhaled by 16 patients with asthma in a dose of 1 mg daily for periods up to 24 weeks. No evidence of adrenal suppression was found in these patients as judged by basal cortisol levels. A further group of five patients with asthma inhaled 2 mg daily of beclomethasone dipropionate for periods up to 10 weeks and no evidence of adrenal suppression was found. A separate group of five patients was found to respond to increasing doses of beclomethasone dipropionate by increasing their forced expiratory volume in the first second. The results suggest that increased doses of beclomethasone dipropionate may provide additional benefit while continuing to avoid unwanted systemic side effects.

Beclomethasone dipropionate is a topically active corticosteroid (Caldwell *et al.*, 1968) which is now used in inhaled form for the treatment of bronchial asthma. In doses of 400 μg daily it does not appear to suppress the pituitary–adrenal axis (Clark, 1972; Lal *et al.*, 1972; Morrow Brown, Storey, and George, 1972; Gaddie *et al.*, 1973). It was shown by these studies that patients could be safely transferred from oral corticosteroid therapy to beclomethasone dipropionate by inhaler, and a further study showed good recovery of adrenal function in patients whose treatment had been thus altered (Maberly, Gibson and Butler, 1973). However, Choo-Kang, Cooper, Tribe, and Grant (1972) found that beclomethasone dipropionate, in a dose of 2 mg daily by inhalation, had no advantage over prednisolone, 20 mg daily orally, and that this dose of 2 mg of beclomethasone dipropionate caused significant adrenal suppression within six days in five of their seven patients. Gaddie *et al.* (1973) could find no evidence of dose response in 15 patients in whom they increased the dose by 29-day increments of 400 μg, from 400 μg daily to 1600 μg daily.

This paper reports the effect of 1 mg daily of beclomethasone dipropionate by inhalation on adrenal function in 16 patients, and the effect of 2 mg daily in a smaller group. An attempt was made to assess the effect of increasing the dose of beclomethasone dipropionate from 400 μg daily to 1 mg daily in patients who had shown an unsatisfactory response to the smaller dose.

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PATIENTS AND METHODS

Twenty-six patients with asthma were recruited for study; 17 of these patients were negative to skin prick testing with a wide range of allergens and nine had one or more positive skin tests. There were 18 male and eight female patients, and their ages ranged from 17 to 78 years with a mean of 45 years.

Pre-treatment plasma cortisol was measured at 9.00 am in 16 patients who were not receiving systemic corticosteroids but was not measured in the remaining 10 patients who were still taking systemic corticosteroids in the immediate pre-treatment period. The 16 patients were then treated with beclomethasone dipropionate aerosol in a dose of 1 mg per day, the aerosol used delivering 250 μg per shot: 9.00 am plasma cortisol levels were again measured at the end of the first week and at four-weekly intervals thereafter for the duration of treatment. It was not possible to assess all 26 patients throughout the trial period because some restarted systemic corticosteroids or stopped using high dosage beclomethasone dipropionate inhaler.

Five of the patients studied had already been inhaling beclomethasone dipropionate in a dose of 400 μg daily and had shown poor response clinically. Their progress on 1 mg daily was compared with their response to the lower dose and was judged in terms of clinical features and forced expired volume in one second (FEV_1).

A further group of five patients inhaled 2 mg of beclomethasone dipropionate daily, and measurements of basal cortisol were made at intervals. A tetracosactrin stimulation test, using 0·25 mg tetracosactrin intramuscularly (Wood *et al.*, 1965), was performed on five patients who had inhaled 1 mg of beclomethasone dipropionate daily for more than eight weeks.

Plasma cortisol (plasma 11-hydroxycorticosteroid) was measured by the method of Mattingly (1962).

RESULTS

Pre-treatment and subsequent levels of 9.00 am plasma cortisol in patients inhaling 1 mg daily are shown in Fig. 1. This illustrates that there was no significant adrenal suppression in patients inhaling this dose for up to 24 weeks.

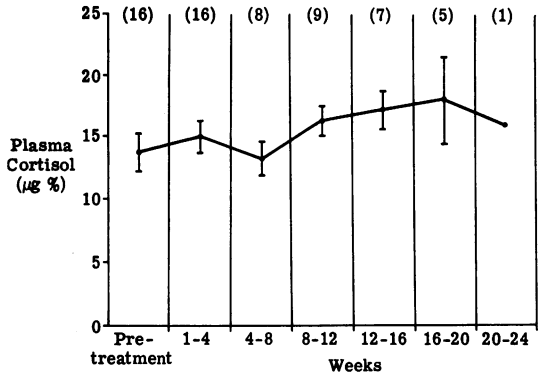

FIG. 1. *Mean 9.00 am plasma cortisol, with standard error of the mean, in patients on 1 mg of inhaled beclomethasone dipropionate daily. The figures in parentheses indicate the number of patients studied in each period as it was never possible to study the whole group together (see text).*

Figure 2 illustrates the 9.00 a.m. plasma cortisol results in the group of five patients who inhaled 2 mg of beclomethasone dipropionate per day, and no evidence of adrenal suppression can be seen over the period of study.

Figure 3 shows a normal response to tetracosactrin stimulation in five patients who had inhaled 1 mg of beclomethasone dipropionate daily for at least eight weeks. Each test fulfils the criteria for a normal tetracosactrin response, i.e., the basal plasma cortisol exceeded 5 μg/100 ml, the increment in plasma cortisol after 30 minutes exceeded 7 μg/100 ml, and the plasma cortisol of the second specimen exceeded 18 μg/100 ml in each case.

In Fig. 4 the increase in FEV_1 in five patients whose dose had been increased from 400 μg to 1 mg daily of inhaled beclomethasone dipropionate can be seen. (This mean FEV_1 is the mean of at least three readings taken over a period of four weeks.) There is no significant difference between the mean values obtained from

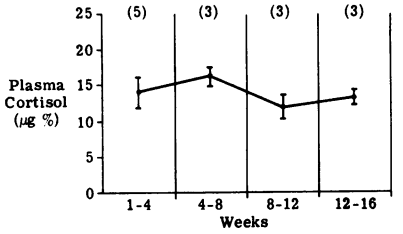

FIG. 2. *Mean 9.00 am plasma cortisol, with standard error of the mean, in patients on 2 mg of inhaled beclomethasone dipropionate daily. The figures in parentheses indicate the number of patients studied in each period. (Two of the patients studied in the first four weeks were able to lower their dose and therefore were not eligible for subsequent study.)*

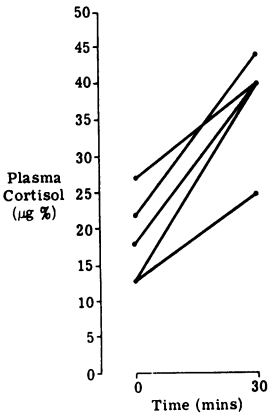

FIG. 3. *Response to tetracosactrin stimulation in five patients who had inhaled 1 mg of beclomethasone dipropionate daily for more than eight weeks.*

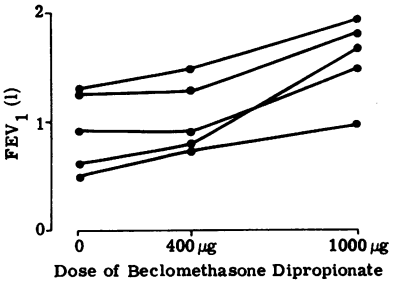

FIG. 4. *Serial mean FEV_1 readings in five patients with asthma on increasing doses of beclomethasone dipropionate.*

patients on no treatment and those on 400 μg daily. However, the difference between the mean pre-treatment FEV_1 and the mean FEV_1 readings recorded when the patients were inhaling 1 mg daily is significant at the 1% level.

DISCUSSION

Most previous studies of beclomethasone dipropionate by inhalation should not be given in 300–400 μg daily (Clark, 1972; Lal *et al.*, 1972; Morrow Brown *et al.*, 1972; Gaddie *et al.*, 1973). There is no reason why beclomethasone dipropionate by inhalation should not be given in varying doses in accordance with the patient's requirements as is customary with systemic corticosteroid therapy. This assumes that benefit will accrue from increasing the dose, but Gaddie *et al.* (1973) failed to find any evidence of a dose response in their study. However, these patients were not selected on the basis of poor response to the low dose, and it is possible that their asthma was such that 400 μg daily was sufficient to control it. Our five patients who had their dose increased from 400 μg daily to 1 mg daily showed evidence of improvement, in terms of both FEV_1 and clinical state, and were selected on the basis of their poor response to 400 μg daily.

ADRENAL FUNCTION This study shows that no adrenal suppression occurs in patients on long-term daily treatment with 1 mg of beclomethasone dipropionate by inhalation. Our results also show that daily doses of 2 mg of beclomethasone dipropionate over prolonged periods do not necessarily cause adrenal suppression and are at variance with the results from Choo-Kang *et al.* (1972). Gaddie *et al.* (1973) showed a reduced response to tetracosactrin in patients inhaling 1·6 mg daily, and it is likely that 1·5–2·0 mg represents the upper limit of dose that is wholly topical.

In summary, our results suggest that higher doses of beclomethasone dipropionate can be used by patients whose symptoms reappear while inhaling the standard daily dose of 400 μg or by those who fail to respond satisfactorily to this dose. Doses of 1 mg per day, and possibly up to 2 mg, can be expected to provide added benefit without significant steroid absorption.

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