Substitution of Beclomethasone Aerosol for Oral Prednisolone in the Treatment of Chronic Asthma

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Summary

In a double-blind study 10 patients with chronic asthma received beclomethasone dipropionate 400 μg daily in a Freon propellant from a pressurized dispenser, and 10 patients received the Freon propellant alone. At the start of the trial each patient was receiving long-term maintenance treatment with oral prednisolone in a dose of 7·5 to 15 mg daily. The daily dose of prednisolone was reduced by 1 mg every four weeks and the patient's progress followed by regular clinical assessment and studies of pituitary-adrenal function. The trial was continued until the dose of prednisolone was reduced to zero or until asthmatic symptoms increased to an unacceptable level.

In the 10 patients who received beclomethasone the mean maintenance dose of oral prednisolone was reduced by 5·6 mg/day but in only two cases could this drug be withdrawn completely. In the placebo group the mean reduction in dose was only 1·3 mg, thus there was a significant difference between the two groups ($P < 0.01$). Studies of pituitary-adrenal function showed that a normal adrenal response to tetracosactrin stimulation returned only in the two patients from whom prednisolone was withdrawn.

Hence the addition of beclomethasone dipropionate by inhalation to systemic corticosteroid therapy allows useful reductions to be made in the oral maintenance doses of corticosteroid. Reductions must be made with caution since there is wide individual variation in response to beclomethasone and in only a minority of patients can oral treatment by completely withdrawn.

Introduction

Beclomethasone dipropionate is a synthetic corticosteroid with a high index of topical activity (Caldwell *et al.*, 1968). Administered by inhalation as an aerosol this drug is now being widely used in the treatment of chronic asthma, though its efficacy has not been adequately assessed. In a double-blind crossover trial on 38 steroid-dependent patients Lal *et al.* (1972) found that beclomethasone by inhalation in a dose of 100 μg four times daily was as effective as 7 mg of prednisolone by mouth, and was less apt than oral prednisolone to depress endogenous cortisol production. Clark (1972) in an uncontrolled study of 17 patients found that the same dose of beclomethasone by inhalation could achieve satisfactory control of asthma without producing biochemical evidence of adrenal suppression. Gaddie *et al.* (1973) in a double-blind crossover study (beclomethasone *v.* placebo) of 15 patients with moderately severe chronic asthma who were not receiving systemic corticosteroids reported that while beclomethasone was being given there was an improvement in forced expiratory volume in 1 second (FEV_1) and no significant reduction in plasma cortisol levels. Though the results of these studies seem favourable it is open to question whether the long-term value of a new form of treatment for chronic asthma can be adequately assessed, even on a double-blind basis, if the active drug and placebo are given only for short periods such as two weeks (Gaddie *et al.*, 1973) or even four weeks (Lal *et al.*, 1972). This objection could be met by extending these periods to (say) six months, but this would of course prolong the duration of trials greatly, and increase the problems both of recruiting patients and of maintaining their co-operation.

Another way to test the efficacy of beclomethasone is to try to discover if patients with chronic asthma on regular treatment ment with oral corticosteroids remain well when this treatment is replaced by beclomethasone. A study on these lines has been reported by Brown *et al.* (1972), who concluded that "it is possible to substitute this therapy (beclomethasone by inhalation) for long-term oral steroids, even when taken for many years" and that "effective control of the asthma is achieved with no evidence of systemic absorption or of steroid side effects." The design of this study and the conclusions drawn from it are, however, open to objection on several counts (Grant *et al.*, 1972). Perhaps the most important criticism stems from the fact that the study was uncontrolled. The authors seemed to assume that because many of their patients remained well after beclomethasone by inhalation was substituted for oral prednisolone the two treatments were equally effective, and they failed to take into account the possibility that the same results might have been achieved if their patients, before the change in treatment, were being given prednisolone unnecessarily or in a higher dose than they needed. A trial of this type should therefore include a control group, and be conducted on a double-blind basis.

With these considerations in mind a clinical trial was designed in which two groups of patients with chronic asthma on regular oral treatment with prednisolone were given either a beclomethasone dipropionate or a placebo aerosol while the dose of prednisolone was being gradually reduced. The minimum effective dose of prednisolone in the two groups was compared. Tests of adrenal and pituitary function were used to discover if pituitary-adrenal function improved when it was possible to reduce the dose of oral prednisolone to below 5 mg/day.

Patients and Methods

Twenty patients with chronic asthma were included in the study. All had been receiving regular treatment with oral prednisolone in a dose of not less than 7·5 mg a day for at least four years. The maintenance dose on entry to the trial ranged from 7·5 mg to 15 mg/day (mean 10·4 mg) and had not been altered during the previous three months.

The patients were allocated at random to two groups of 10. Those in the beclomethasone group were issued with pressurized dispensers which delivered a metered dose of 50 μg of beclomethasone dipropionate aerosol suspended in a Freon propellant, and those in the control group with identical dispensers delivering the propellant alone. All patients were

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instructed to inhale two metered doses four times daily. After a preliminary period of four weeks, during which no change was made in the maintenance dose of oral prednisolone, the dose was reduced by 1 mg/day, and the same reduction was then made at intervals of four weeks either until the dose was down to zero or until it was thought necessary to withdraw the patient from the trial. If a patient developed a severe recurrence of asthma the dose of oral prednisolone was increased to 20 mg/day for 5-7 days. The maintenance dose of prednisolone was then held for a further period of four weeks at the level at which deterioration occurred. If, during this period, there was a second recurrence of asthma requiring an increase in the dose of prednisolone the patient was withdrawn from the trial.

The minimum effective dose of oral prednisolone was defined as the dose taken for four consecutive weeks before it was reduced to the level at which the patient had to be withdrawn from the trial. For example, if supplementary treatment with prednisolone was required on two occasions while the maintenance dose was at 4 mg/day the minimum effective dose was recorded as 5 mg/day. Similarly, a minimum effective dose of zero was recorded only if, at the end of the trial, a patient completed a four-week period without prednisolone.

The following daily recordings were made by each patient on a diary card: (1) severity of symptoms; (2) frequency of salbutamol inhaler usage; and (3) dose of prednisolone. Every patient was reviewed by the co-ordinator of the trial (E.J.C.) at four-week intervals, when the dose of prednisolone was due to be reduced. At these visits the diary card was scrutinized and the FEV_1 was recorded before the next reduction in dose was sanctioned. If deterioration occurred between routine visits the patient was seen immediately by the trial co-ordinator, and a decision was made on the basis of the clinical findings and on the level of FEV_1 whether to increase the dose of prednisolone to 20 mg/day for a 5-7 day period.

On entry to the trial plasma cortisol was measured at 9 a.m. and 10.30 p.m., and a tetracosactrin test was carried out. The same procedure was repeated in all patients after the dose of prednisolone had been at 5 mg daily for four weeks, and then at intervals of eight weeks until the dose was reduced to zero, or until the patient was withdrawn from the trial. In addition, patients who were able to discontinue prednisolone had a further tetracosactrin test two months later.

In all patients withdrawn from the trial because of a recurrence of asthma a standard beclomethasone aerosol was substituted for the trial preparation, and a further attempt was made to reduce the dose of oral prednisolone by 1 mg/day at four-week intervals. It was hoped in this way to determine whether patients in the control group would be able to reduce the dose of oral prednisolone when they were treated with beclomethasone.

Results

The patients treated with beclomethasone dipropionate reduced their oral dose of prednisolone more than those treated with a placebo aerosol (see table). Two patients, both receiving beclomethasone, were able to discontinue prednisolone. The mean reduction in daily prednisolone dosage was 5·60 mg (range 2-10 mg) in the beclomethasone group and 1·35 mg (range 0-3·5 mg.) in the placebo group. It is valid to compare these two groups, since the trial was double-blind, but the mean reductions cannot be compared using the usual t-statistic with 18 degrees of freedom because the variance of the reductions for the placebo group is much smaller than that for the beclomethasone group. Nevertheless, the Behrens-Fisher statistic (4·48 for this data) can be closely approximated by the t-statistic on 9 degrees of freedom. With this test the difference between the mean reductions is found to be highly significant ($P < 0·01$).

During the trial patients continued to use a salbutamol inhaler when necessary. The use of this β-adrenoreceptor stimulant was recorded daily by each patient, and the total number of inhalations in the four-week periods corresponding to the initial dose and minimum effective dose of prednisolone are shown in the table. While five patients appreciably increased their use of salbutamol on the minimum effective dose of prednisolone, analysis showed that inhaler usage was not significantly different for the two periods in either the beclomethasone or placebo group. The similarity of salbutamol usage in most individuals suggests, indirectly, that symptoms were well controlled on the minimum effective dose of prednisolone.

TABLE I—*Oral Prednisolone (mg/day) and Salbutamol Inhaler Usage*

Case No.	Prednisolone Doses (mg/day)			Frequency of Salbutamol Inhaler Usage during 4-week Periods	
	Initial	Minimum Effective	Reduction	During Initial Dose of Prednisolone	During Minimum Effective Dose of Prednisolone
			Beclomethasone Group		
4	10	0	10	87	98
5	10	5	5	85	133
7	11	5	6	11	12
10	10	7	3	0	0
11	10	0	10	55	51
13	10	4	6	15	26
14	15	12	3	181	170
16	10	8	2	44	56
18	13	8	5	4	2
20	10	4	6	36	40
			Placebo Group		
1	8·5	8	0·5	81	57
2	8	5	3	46	56
3	10	8	2	64	126
6	10	9	1	77	77
8	10	10	0	65	—
9	7·5	6	1·5	12	2
12	15	13	2	90	61
15	9	9	0	0	—
17	12·5	9	3·5	109	110
19	7·5	7·5	0	288	—

As a subsidiary investigation all patients withdrawn from the trial were given known beclomethasone and further reduction in the dose of prednisolone was attempted using the original trial method. When the code was broken at completion of the trial it was found that the substitution of known beclomethasone in the group of eight patients who had already received this drug allowed little or no further reduction in prednisolone dosage (mean further reduction 0·5 mg, range 0-2 mg). Nevertheless, known beclomethasone allowed three of the 10 patients in the original placebo group to discontinue oral prednisolone and four others to reduce the dose by at least 5 mg (mean reduction 4 mg, range 0-8 mg). These results are similar to those achieved in the double-blind trial.

BIOCHEMICAL STUDIES

On entry to the trial all 20 patients (who were receiving oral prednisolone in a dose of at least 7·5mg daily) had low resting plasma cortisol levels (less than 4 μg/100 ml), no diurnal variation, and no response to tetracosactrin stimulation. In the placebo group all 10 patients were withdrawn before the dose of prednisolone was reduced below 5 mg daily and all 10 patients had low plasma cortisol levels, no diurnal variation, and no response to tetracosactrin at the time of withdrawal.

In the beclomethasone group four patients were withdrawn when the daily dose of prednisolone was 7 or 8 mg; in these patients the resting plasma cortisol remained low and diurnal variation was absent. When the dose of prednisolone was reduced to 5 mg daily in the remaining six patients, higher morning basal plasma cortisol levels (range 3-12 μg/100 ml) were recorded. In four of these six patients tetracosactrin tests showed an increase in plasma cortisol, but in none was the increase greater than 6 μg/100 ml. In the two patients who were able to discontinue oral prednisolone a normal response to tetracosactrin was recorded in both cases within two months.

In the subsidiary open study of known beclomethasone small increases in plasma cortisol (less than 6 μg/100 ml) to tetracosactrin were recorded in five of seven patients when the dose of prednisolone was reduced to 5 mg daily. Two of the three

patients who were able to discontinue prednisolone had normal tetracosactrin tests two months after oral treatment had been completed.

Discussion

In this double-blind study of 20 patients with chronic asthma the addition of beclomethasone by inhalation in a dose of 100 μg four times daily permitted a mean reduction of 5·6 mg in the oral maintenance dose of prednisolone, as compared with a mean reduction of only 1·3 mg/day in the control group. This difference is statistically significant. The dose of prednisolone was reduced by 5 mg/day or more in seven of the 10 patients who received the active preparation. In only two of these seven patients, however, could prednisolone be withdrawn completely. Analysis of diary card data, including the frequency of salbutamol inhaler usage, showed that satisfactory control of asthmatic symptoms was maintained in the two patients who were able to discontinue prednisolone and also in the other eight patients until they were withdrawn from the trial. The negligible reduction in the maintenance dose of prednisolone in the control group indicates that the patients who participated in the trial were not receiving unnecessarily high maintenance doses of this drug. A control group was not included in previously reported beclomethasone trials of a similar nature (Brown *et al.*, 1972; Maberly *et al.*, 1973), and our main objection to these studies is that some of the reductions in the maintenance dose of prednisolone may have been achieved only because the initial dose was in excess of the patient's requirements.

All patients on withdrawal from this trial were treated with known beclomethasone if it had not been possible to replace prednisolone by beclomethasone. In the control group this permitted reductions of prednisolone dosage of a similar order to those achieved in the beclomethasone group during the double-blind trial. As would be expected, no significant further reductions of prednisolone dosage were possible in patients who had received beclomethasone in the double-blind trial, since they were merely continuing the same treatment. This "open" investigation of beclomethasone thus confirmed the results of the double-blind trial, and at the same time indicated that the active and control groups were well matched.

A cautious approach to the substitution of beclomethasone for prednisolone was adopted deliberately to minimize the risk of producing a dangerous state of pituitary-adrenal insufficiency (Cayton and Howard, 1973). This also averted the unpleasant symptoms which are apt to occur when oral prednisolone therapy is hastily replaced by beclomethasone (Brown *et al.*, 1972; Maberly *et al.*, 1973). All of our 20 patients had complete suppression of pituitary-adrenal function on entry to the trial. Though it was possible to reduce the dose of prednisolone by at least 5 mg/day in seven of the 10 patients in the beclomethasone group, restoration of normal pituitary-adrenal function was observed only in the two patients who were able to stop prednisolone completely. Possibly, however, some of the patients in whom the maintenance dose of prednisolone was substantially reduced will, in time, show a similar trend.

Some patients whose asthmatic symptoms were adequately controlled by relatively small doses of predisolone achieved only small reductions in dosage after the introduction of beclomethasone, while others who had required higher doses of prednisolone were able to discontinue this drug completely. These inconsistencies are difficult to explain, but they emphasize the need for a cautious approach to the substitution of beclomethasone for prednisolone, because some patients whose asthma has been well controlled by prednisolone may deteriorate if the dose of that drug is reduced too rapidly during the transition period.

This double-blind trial of beclomethasone in patients on regular treatment with oral prednisolone for chronic asthma confirms that the administration of beclomethasone by inhalation usually permits a substantial reduction in the maintenance dose of prednisolone, though it can replace prednisolone completely only in a few cases. Any reduction in the dose of prednisolone is, of course, to the patient's advantage, because it reduces the incidence of systemic side effects. Beclomethasone dipropionate by inhalation can, therefore, be regarded as a valuable addition to the measures at present available for the treatment of chronic asthma.

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