Beclomethasone dipropionate and Betamethasone valerate with Sodium cromoglycate in Steroid-dependent Asthma in Adults*

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SUMMARY Sixty-eight steroid-dependent asthmatics with severe complications resulting from long-term oral steroid therapy were studied in an attempt to find a way to wean them gradually off the oral steroids. A combination of beclomethasone dipropionate or betamethasone valerate aerosol was used along with sodium cromoglycate powder, intermittent positive-pressure delivery of L-acetyl cysteine and salbutamol, and ACTH. The period of follow-up was three years. Long-term results on the whole, were disappointing. Patients over 40 years of age, who had been taking steroids for more than three years or in doses exceeding 15 mg of prednisolone daily could not be satisfactorily controlled beyond three to four months.

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Steroid dependence is induced in asthmatics through the continued use of oral steroids usually for a year or more.[1] Simultaneously, they develop hyperacidity, recurrent respiratory tract infection, osteoporosis, Cushingoid features, etc., along with suppression of adrenal function.[2] It has been claimed that most of these cases can be maintained on topically acting steroid aerosols such as beclomethasone dipropionate (BDP) or betamethasone valerate (BV).[3,4] However, such recommendations have been based on short-term studies.[3-5]

Long-term studies on children and adults are very few.[1,6,7] This prospective long-term study involved a planned schedule of oral steroid withdrawal and replacement by steroid inhalation therapy in steroid-dependent asthmatics.

MATERIALS AND METHODS

During the period 1976 – 1981, sixty-eight steroid-dependent patients (Tables 1 & 2) who had reversible airway obstruction (a 15% or more increase in FEV_1 following inhalation of a metered dose of salbutamol or orciprenaline with or without the addition of steroid) were selected for this study. All had a history of steroid therapy ranging from three to 10 years or more (Tables 2 & 3) with resultant complications.

Clinical assessment of the patients was accomplished by using a detailed history and mathematical scoring of signs and symptoms as a scoring index (SS score).[1] Tablet scoring was done by counting the number of bronchodilator tablets consumed per week; a 4-mg salbutamol tablet (Ventolin®) was considered as one unit.

Laboratory investigations included routine blood, stool and urine examinations, throat and nasal swabs for culture, antibiotic sensitivity test, and nasal smear for eosinophil count; also taken were postero-anterior radiographs of the chest, pulmonary function tests (FVC, $FEV_{1.0}$, MVV, PEFR and FEV_1/FVC ratio using Wright's respirometer, expirograph and peak flow meter) at rest and after mucolytic (L-acetyl cysteine) and bronchial antispasmodic inhalation (salbutamol); skin allergy tests using Merck, Bencard and Curewel allergens, and standard 12-lead electrocardiography. For assessment of the hypothalamo-pituitary-adrenal (HPA) axis, antispasmodics and corticosteroids were omitted for 12 and 24 hours respectively; plasma cortisol was estimated at 9 a.m. daily by Mattingly's fluorimetric method.[8] Urinary 17 ketosteroid and 17-oxyhydrocorticosteroid (24 hours)

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Table 1 Criteria of steroid dependence

1. Uninterrupted steroid intake for more than one year (rarely occurs before six months).
2. Sign and symptom score of asthma worsening on temporary stopage of steroids.
3. No immediate improvement in sign and symptom score after giving a double dose of antispasmodics after steroid withdrawal.
4. Precipitation of symptoms of steroid withdrawal e.g. lethargy, headache, weakness, pseudorheumatism, emotional disturbances, etc. after stoppage of steroids.
5. Decreased FEV_1/VC ratio, EPF and other pulmonary functions (even evidence of RAO may be absent) on steroid withdrawal.
6. No substantial improvement in these parameters after continuous oral or parenteral administration of bronchodilators.
7. Reasonable improvement following 2-3 times the previous daily dosage of steroids as shown by:–
   a. Reduction of asthma sign and symptom score
   b. Alleviation of general withdrawal symptoms
   c. Improvement of pulmonary functions
   d. Increase of reversibility.

Table 2 Age vis-a-vis steroid dosage

No. of patients	Age group (yrs)	Steroid dosage (duration) 3-5 hrs	5-10 yrs	> 10 yrs	M : F
40	⩾40	3	10	7	15 : 5
	<40	1	10	9	11 : 9
6	>40	1	1	0	0 : 2
	<40	0	4	0	3 : 1
12	>40	0	2	2	2 : 2
	<40	0	3	5	5 : 3
7	>40	0	0	1	1 : 0
	<40	0	5	1	1 : 5
3	>40		0	0	0 : 0
	<40	0	1	2	3 : 0
Total 68		5	36	27	41 : 27

Table 3 Dosage of steroids used before trial

Body wt. (kg)	No. of cases	Dosage of steroid (prednisolone equivalent – mg per day)
>50	40	15 or more
	6	10 – 12.5
>40 – 50	12	10
30 – 40	7	10
<30	3	10

were measured by the usual modified Vestergaard method; ACTH stimulation was provided by using 20-40 units of long-acting ACTHAR gel twice daily for three successive days followed by re-estimation of the aforementioned parameters. A rise of 7 μg or more of plasma cortisol over basal levels or a level of 20 mg or more per day of urinary ketogenic steroid was taken to indicate an intact HPA-axis.[9]

For oral steroid withdrawal, these patients were placed on a predetermined schedule whereby L-acetyl cysteine (1 ml of 20% solution) and salbutamol were given by IPPB using Bird's respirator.[10,11] When the SS score improved by 25-30 per cent and PEFR reached 60 per cent of the expected normal, the daily administration of 40-80 mg of sodium cromoglycate (SCG) was begun in view of its steroid-sparing effect.[2,12,13] Between the second and fourth weeks, the oral steroid dosage was reduced by half a tablet weekly or fortnightly or over an even longer period (2.5 mg of prednisolone equivalent). The administration of BDP/BV at 200-400 μg/400-800 μg respectively per day was followed at the same time by periodic ACTH injection. Infective episodes or situations of stress were covered as a *precautionary* measure by using low-dose oral steroids for a few days.[9,14]

For the first three months, patients were followed up weekly; SS score, pulmonary functions, tablet score, steroid dosage, etc., were checked as part of follow-up. Subsequently, the patients were examined monthly or every two months for the first year; thereafter, quarterly check-ups were done for two years. All through this period, patients were monitored closely for evidence of candidiasis in the form of erythema or white patches inside the buccal cavity and in swabs sent for microbiological examination.

Those cases were considered a *success* in whom oral steroids could be stopped. Steroid dosage could

be cut down to about half the previous dosage in all cases. Cases requiring periodic oral steroid supplements to control acute spasms were regarded as *partial successes*. Patients experiencing frequent exacerbations even on oral steroids and BDP/BV were regarded as failures (Fig. 1).

RESULTS

The results have to be assessed in the light of the fairly large number of irregularities at regular intervals (Table 4), which, on further enquiry (by health visitors, personal communication and enquiry by post) always revealed a failure of the BDP/BV treatment.

First year : All patients completed the first three months of the trial. However, complete steroid withdrawal was possible in seven cases, five of whom had received daily 15 mg or less of prednisolone or its equivalent; the remaining two patients received higher dosages. Other cases (61 patients) required steroids at a reduced dosage.

Three patients died in the 5th, 19th and 24th weeks due to respiratory failure, which resulted from status asthmaticus in two of the cases and chest infection in the remaining one. Nine patients had stopped coming to the clinic; of that number, six were definite cases of failure, as revealed on further enquiry. Thus, at the end of the first year, attendance was 56.

Second year: Attendance was 39 with five of the cases being successful. Two deaths occurred at home due to unknown causes and 15 patients, who were lost to follow up, were regarded as failures (as revealed in 10 cases on further enquiry). Out of seven initially successful cases, two started to take steroids orally when withdrawal symptoms became troublesome.

Third year: Success was maintained in the same five cases. One patient died at home due to an unknown cause. There were 11 dropouts (as revealed in five cases on enquiry) and these were considered as failures.

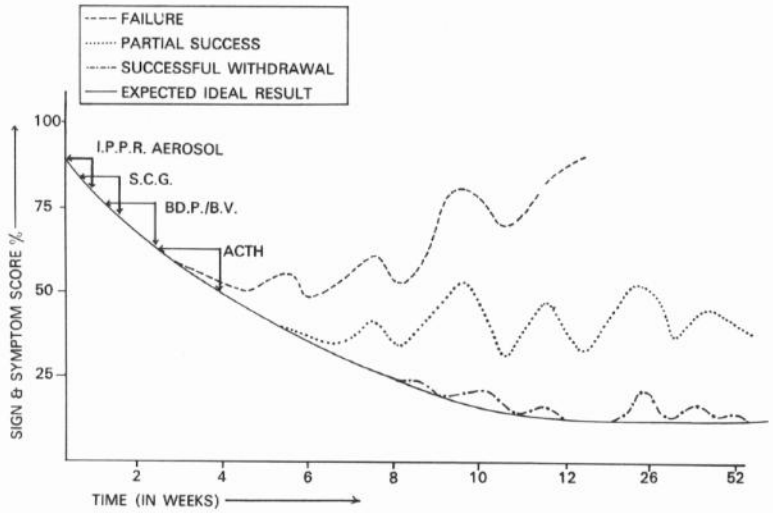

Fig. 1 A schematic representation of the steroid withdrawal schedule and the results obtained (sign & symptom score 100% = 64)

Table 4 Results at the end of each three successive years (n = 68)

Follow – up	Success	Partial success	Failure			
			Seen	CE	Total	Death
End of 1st yr (n = 56)	7	23	26	6 (9)	35	3
End of 2nd yr (n = 39)	5	17	17	16 (24)	41	5
End of 3rd yr (n = 27)	5	14	8	21 (35)	43	6

CE : Confirmed by enquiry; figures in parentheses denote total dropouts

Table 5 Influence of age and sex on the results of treatment*

	Success		Partial success		Failure		Subtotal		Total
Age in yrs.	<40	$\geqslant 40$	<40	$\geqslant 40$	<40	$\geqslant 40$	<40	$\geqslant 40$	
Male	2	1	9	3	5	11	16	15	31
Female	3	1	6	5	0	10	9	16	25
Total No.	5	2	15	8	5	21	25	31	56

*At the end of the first year. (n = 56)

After evaluation of the results, several factors were found to be of significance:

*1. **Age** :* Most of the successful cases belonged to the younger age group (Table 5).

*2. **Sex** :* On the whole, females fared better than males (Table 5).

*3. **Duration of steroid treatment**:* It was not found to be of much influence when it was used continuously for more than five years (Table 6).

*4. **Dose of steroid** :* 15 mg or more of prednisolone daily gave poor results.

*5. **State of asthma** :* Patients with controlled asthma (i.e. with a score

Table 6 Inflence of the duration of previous steroid therapy on withdrawal*

Duration (yrs)	Success	Partial success	Failure	Total
3 – 5	2	3	0	5
5 – 10	4	13	9	26
> 10	1	7	17	25
No. of cases.	7	23	26	56

*At the end of the first year.

of 30 per week or lower; five cases out of 18 showed favourable response) had more success than those with uncontrolled asthma or frequent acute flare-ups (two successes out of 38).

*6. **Tablet score** :* As an additional point of interest, all successful and partially successful cases had a significant reduction in tablet consumption. The initial score of 29.6 ± 4.9 came down to 11 ± 1.4 per week ($p < 0.01$).

*7. **Peak-flow values** :* 12 cases with very low PEFR (100 litres/min.) fared worse than 17 with higher values (200 litres/min.). There was no significant correlation in the intermediate range.

*8. **FEV_1/FVC ratio** :* those having figures of 40 per cent or less tended to have poor results (two cases). There was no significant correlation in the higher values range.

*9. **Plasma cortisol and urinary ketogenic steroids** :* Surprisingly nine cases with a responsive HPA-axis did not fare significantly better than the 13 with an apparently non-responsive HPA-axis. Three cases with an apparently normal HPA-axis died.

*10. **Oral candidiasis**:* In nine cases showing erythema with white spots on the pharyngeal wall, swab cultures were negative for *Candida*. No other case showed any clinical evidence of candidiasis.

DISCUSSION

The results presented in our study indicate that complete withdrawal from oral steroids is difficult when patients are over 40 years of age, taking more than 15 mg of prednisolone for more than three years, or have unstable asthma with frequent acute attacks. However, in these difficult cases, oral steroids can always be reduced by 25-50 per cent and replaced with aerosol steroids. The hope for a complete switch-over to BDP/BV seems to fade when long-term replacement therapy is considered. Our results are in agreement with those of previous reports,[6,7] i.e., that long-term high dosage oral steroids (16 mg/day of prednisolone) may not be replaced fully by aerosols. However, oral steroid withdrawal for short periods is possible in a fair number of cases.[3-5]

Re-institution of oral steroid therapy was necessary for the partially successful group, mostly to counteract the severe withdrawal symptoms which were difficult to control with inhalant steroids,[2] even though the asthmatic process could be kept in remission. Increasing the steroid aerosol dose (beyond 16 puffs daily) in the cases of failure was not attempted because the administration of 1,600 μg/day or more of BDP has been shown to cause adrenal suppression[2,15] and because previous investigations[15-17] have shown that a higher dosage does not improve the results in such cases.[15,17] The rarity of oropharyngeal candidiasis in India compared with the West,[16] has also been noted in another short-term study.[18] This remarkably low incidence may be explained by national food habits, routine cleaning of the mouth after every meal and avoidance of sweets between meals.

Our results on adult asthma in this study are in contrast to the results on children previously reported.[1] It is possible that children have highly responsive adrenal glands, which are able to resume their function even after two years of continuous steroid therapy. In our opinion, steroid-dependent asthma in adults is very difficult to control by aerosol therapy alone. A very slow steroid withdrawal (taking 6-12 months) is being tried at present.

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REFERENCES

1. Gupta SK, Chatterjee S, Mitra K. Beclomethasone dipropionate and betamethasone valerate with sodium cromoglycate in steroid-dependent asthma in children. J Assoc Phys India 1984; 32:245-9.
2. Clark TJH. Corticosteroids. In: Clark TJH, Godfrey S, eds, Asthma. London: Chapman & Hall, 1977:286-302.
3. Brown MH, Storey G, George WHS. Beclomethasone dipropionate: A new steroid aerosol for the treatment of allergic asthma. Brit Med J 1972; 1:585-90.
4. Lowell LH, Nair VS, Kass I. Beclomethasone dipropionate aerosol in the treatment of steroid-dependent asthma. A 12 week double blind study comparing beclomethasone dipropionate and vehicle aerosol. Chest 1976; 70:345-50.
5. Hodson ME, Batten JC, Clark S, Gregg I. Beclomethasone dipropionate aerosol in asthma. Transfer of steroid-dependent asthmatic patients from oral prednisolone to beclomethasone diproprionate aerosol. Am Rev Respir Dis 1974; 110:403-8.
6. Brompton Hospital / Medical Research Council Collaborative Trial. Double-blind trial comparing two dosage schedules of beclomethasone dipropionate aerosol in the treatment of chronic bronchial asthma. Lancet 1974; 2:303-7.

7. Brompton Hospital / Medical Research Council Collaborative Trial: Double-blind trial comparing two dosage schedules of baclomethasone dipropionate aerosol with a placebo in bronchial asthma. Brit J Dis Chest 1979; 73:121-32.
8. Mattingly D. A simple fluorimetric method for the estimation of free 11-hydroxycorticosteroid in human plasma. J Clin Path 1964; 8:374-9.
9. Jones RS. Asthma in children. London: Edward Arnold, 1976:143-56.
10. Gupta SK. Salbutamol – mucolytic aerosol therapy in status asthmaticus. J Ind Med Assoc 1974; 62:158-60.
11. Gupta SK. Five year follow-up of controlled study of perennial bronchial asthma (extrinsic type) with sodium cromoglycate, and respirator using mucolytics and antispasmodics. Indian Pract 1981; 24:27-34.
12. Chai H, Molk CJ, Miklich D. Steroid sparing effect of disodium cromoglycate in children with severe chronic asthma. Proc VII Internat Congr Allergology. Excerpt Med 1970; 232:385-91.
13. Brogden RN, Speight TA, Avery CS. Sodium cromoglycate (cromolyn sodium): A review of the mode of action, pharmacology, therapeutic efficacy and use. Drug 1974; 7:164-282.
14. Godfrey S, König P. Treatment of childhood asthma for 13 months and longer with beclomethasone dipropionate aerosol. Arch Dis Childh 1974; 9:591-6.
15. Gaddie J, Petrie GR, Reid IW, Sinclair DJM, Skinner C, Palmer KNV. Aerosol beclomethasone dipropionate: a dose response study in chronic bronchial asthma. Lancet 1973; 2:280-1.
16. Sahay JN, Chatterjee SS, Stanbridge TN. Inhaled corticosteroid aerosol and candidiasis. Brit J Dis Chest 1979; 73:164-7.
17. Kennedy MGS, Posner E, Thursby-Pelham DC. The efficacy of beclomethasone dipropionate aerosol either alone or combined with adrenergic or cromoglycate aerosol in the treatment of asthma. In: Viswanathan R, Jaggi OP, eds, Advances in chronic obstructive lung disease. Delhi: Asthma and bronchitis foundation of India, 1977:453-9.
18. Kulpati DDS, Kinra V, Kamath RK, Chauhan MR. Betamethasone valerate aerosol in steroid dependent patients with reversible airway obstruction. Ind J Chest Dis 1981; 23:116-20.