EVALUATION OF SODIUM CROMOGLYCATE B.P. (INTAL) IN THE PROPHYLAXIS OF BRONCHIAL ASTHMA IN ASIANS

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SYNOPSIS

A double-blind cross-over trial was undertaken to determine the prophylactic value of sodium cromoglycate B.P. in patients of Asian stock with bronchial asthma. Statistical analysis of the results showed the drug was superior to placebo in reducing:—

(a) the number of acute asthmatic attacks;

(b) the bronchodilator requirement

The majority of the patients at the end of trial period preferred the drug to the placebo. Slight improvement in the Forced Expiratory Volume in one second was obtained at the end of the drug period.

INTRODUCTION

Sodium cromoglycate B.P. (SCG) has been shown to be of prophylactic value in patients with bronchial asthma but most of the clinical trials were undertaken in Caucasians (Howell *et al*, 1967; Campbell *et al*, 1969; Gianoustos *et al*, 1969). Whether SCG is of equal prophylactic value in Orientals is not known. In order to find out the effect of SCG in patients of Asian stock, a double-blind cross over trial was undertaken using active drug and placebo in random sequence.

MATERIAL AND METHOD

47 patients entered the trial but only 37 completed the trial. No attempt was made to separate patients with asthma of extrinsic etiology from those of intrinsic etiology (Bromton hospital and M.R.C. Trial, 1972). There were 20 males and 17 females. 25 of these were Chinese, 8 Indians and 3 Malays. Most patients were initially stabilised as outpatients with bronchodilators. Forced Expiratory Volume in one second (FEV_1) and Vital capacity (VC) were measured for each patient using a single breath wedge spirometer, 'Vitalograph', model, and the results expressed as a percentage of $\frac{FEV_1}{VC}$ ratio $\frac{FEV_1}{VC} \times 100$). The details of the patients are given in Table I. The medication was dispensed in capsules. The active capsules contained sodium cromoglycate B.P. 20 mg. and Lactose 20 mg. The placebo contained anhydrous sodium sulphate 5 mg. and lactose 35 mg. The patients were instructed on the correct use of the spinhaler by use of which the contents of the capsule are inhaled. Each patient was asked to inhale one capsule four times a day. In one 8-week period the capsules contained SCG and in other, the placebo. The patients were reviewed by both of us every 4 weeks. In the intervening period they were asked to keep a record of the number of asthmatic attacks and the amount of bronchodilators consumed. For the mild attacks they were asked to use either a bronchodilator aerosol or sublingual Isoprenaline. They were also asked to increase the oral bronchodilator tablets if they had frequent wheezing attacks. For the moderate and severe attacks they were asked to report to our hospital's outpatient or casualty department for adrenaline injections.

If there was no response to adrenaline or if the attending doctor thought the attack was severe enough, the patient was admitted for inpatient treatment. In this way accurate data were available on the number of visits for adrenaline injections for the moderate attacks and the number of hospital admissions for the severe attacks. At the end of each 8-week period,

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TABLE I

Age distribution in years	11—20	21—30	31—40	41—53
No. of patients	6	14	9	8
Mean duration of Asthma in years	8·76	15	16·44	17·5
Mean Hospital Admission rate	3·16	2·7	2·5	3·9
MEAN $\frac{FEV_1}{VC} \times 100$	57·1	57	54·5	54·12

a clinical assessment was made and FEV_1 measured for each patient. Each patient was also asked to state his preference, i.e. whether he would prefer to continue treatment with the capsules taken in the first 8-week period or the second 8-week period. The order of treatment was not known to any of us until the final assessment was completed.

RESULTS

Number of mild attacks: 29 patients out of 37 had less attacks while on the drug compared to the placebo, and only 8 patients out of 37 had more attacks while on the drug compared to the placebo. Statistical analysis was done by testing the significance between the means of the number of mild attacks. The result showed the drug superior to placebo in reducing the number of mild attacks. The difference was significant at 99·7% level.

Oral bronchodilator requirement: Table II gives the requirement for the drug and placebo periods. During the trial period they were increased in 8% of the patients, decreased in 14% and remained the same in 78%. Statistical analysis of these results was done by the 'Chi' square test, and the results were significant, $0{\cdot}001 < P < 0{\cdot}01$. The variations obtained could not be due to chance. We conclude the drug was more effective in reducing bronchodilator requirement than the placebo.

TABLE II

ORAL BRONCHODILATOR REQUIREMENT

Bronchodilator requirement	On Drug	On Placebo	Total
Increased	1	5	6
Decreased	10	0	10
Same	26	32	58

Increased = 8% Decreased = 14% Same = 78%

$X^2 = 13$ $0{\cdot}001 < P < 0{\cdot}01$

Analysis of Hospital visits for adrenaline injections: Table III, there were only 21 visits for adrenaline during the drug period compared to 81 visits during the placebo period. It is quite obvious from these figures, the drug was more effective in reducing the number of hospital visits for adrenaline injections.

TABLE III

NUMBER OF HOSPITAL VISITS FOR ADRENALINE INJECTIONS

Drug Period	Placebo Period
21	81

Preference: Table IV gives the preference for the drug and placebo. 24 out of 37 (65%) preferred the drug whereas only one out of 37 (3%) preferred the placebo. Twelve out of 37 were not able to state their preference, 2 of these (12%) preferred both, and 10 preferred neither. Thus the majority of patients preferred the drugs.

TABLE IV

PREFERENCE

Drug/Placebo	No.	%
Drug	24	65
Placebo	1	3
Both	2	5
Neither	10	27
TOTALS	37	100

Number of hospital Admissions: The difference in the number of admissions for the placebo period and the drug period is given in Table V.

TABLE V
NO. OF HOSPITAL ADMISSIONS

Placebo/Drug Difference	No. of Patients	%
During Placebo period number of admissions were:		
(a) Increased	9	24
(b) Decreased	4	11
(c) Remained same	24	65
TOTALS	37	100

During the placebo period they were increased in 9 patients, decreased in 4 patients, and remained the same in 24 patients. We feel the trial period of 16 weeks is too short to draw any statistical conclusion on the number of admissions, as the patients were admitted to hospital only for severe attacks of asthma.

$\frac{FEV_1}{VC} \times 100$: No statistically significant beneficial result for the drug period was obtained if one tested the difference between means of $\frac{FEV_1}{VC} \times 100$. But testing the means of the differences as in Table VI, showed statistically significant results, $P<0{\cdot}001$, whether one tested drug-placebo difference or the drug pretrial-posttrial difference.

No statistically significant result could be obtained by testing the placebo pretrial-posttrial difference, $0{\cdot}05<P<0{\cdot}10$. Although statistical significant improvement in $\frac{FEV_1}{VC} \times 100$ for the drug period was obtained, the objective improvement in the respiratory function did not match subjective improvement shown by the other parameters analysed.

SIDE EFFECTS

Side effects were minimal. Some patients complained of irritation of the throat after inhalation of the contents of the capsule but no patient discontinued treatment on account of these symptoms.

DISCUSSION

Sodium cromoglycate B.P. does not possess any anti-inflammatory or bronchodilator property and it has no anti-histamine or corticosteroid-like activity. It is believed to act by preventing release of broncho-constrictor substances such as histamine, slow reacting substance of anaphylaxis, etc., by stabilization of mast cell membranes (Cox *et al*, 1969). In experimental studies in allergic subjects SCB has been shown to inhibit both type I immediate and type III late antigen induced asthmatic reactions (Altounyan, 1967). Both short-term and long-term clinical trials in Caucasians have shown the drug to be of prophylactic value in patients with bronchial asthma. Although it is most beneficial for patients with extrinsic bronchial asthma, some patients with intrinsic asthma are benefitted as well. In the latter, SCB may permit reduction of corticosteroid requirement (Rend *et al*, 1969).

Thus in clinical practice the only way to find out whether or not a patient will respond is to do a therapeutic trial by prescribing the drug for a limited period (Brogden *et al*, 1974); (N).

TABLE VI
TESTING THE MEANS OF THE DIFFERENCES

	Differences in $\frac{FEV_1}{VC} \times 100$		
	Drug Placebo	On Drug Pretrial—Post-trial	On Placebo Pretrial—Post-trial
Means	2·57 (+)	4·57 (—)	2·00 (—)
Standard Deviation	3·72	7·40	6·20
Standard error	0·61	1·22	1·02
t: (36DF)	4·213	3·745	1·961
Statistical Conclusion	$P<0{\cdot}001$ Highly significant	$P<0{\cdot}001$ Highly significant	$0{\cdot}05<P<0{\cdot}10$ not significant

If the patient's asthma is improved, the drug could then be continued. The results of our double blind crossover trial show SCB to be of prophylactic value in Oriental patients with bronchial asthma. SCB was superior to placebo in reducing:—

(a) number of mild attacks

(b) amount of bronchodilators consumed.

Majority of patients at the end of the trial were able to state their preference for the drug. Beneficial effect of the drug was however least marked in $\frac{FEV_1}{VC} \times 100$ and this has been the experience of others. Side effects were minimal. We conclude SCB is of prophylactic value in Asian patients with bronchial asthma just as it is in Caucasians.

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