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THE CORTICOSTEROID SPARING  
EFFECT OF DISODIUM CROMOGLYCATe  
IN CHILDREN AND ADOLESCENTS  
WITH BRONCHIAL ASTHMA

By

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Disodium cromoglycate (DSCG)\* is a chromone derivative which has been shown by immunological studies in animals to have the effect of interfering in some way with the release of chemical mediators following the union of antigen and reaginic antibody (4). Since 1967 when the first report of the clinical effectiveness of DSCG in bronchial asthma appeared (5), numerous studies have been published reaching the same conclusion that the drug is a major advance in the treatment of bronchial asthma. The statements of the clinical effectiveness of the drug have relied mainly on symptomatic assessment. Among the beneficial effects reported, the one of corticosteroid-sparing has been stressed, among others by Morrison Smith and Devey in children (9). The possibility of this latter effect made us design a long term trial with DSCG to assess whether a corticosteroid-sparing effect can also be shown in children with perennial bronchial asthma severe enough to have required continuous corticosteroid treatment for several years.

The effect of the treatment was assessed solely on the

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\* Trade mark, "Intal", "Lomudal", Fisons Pharmaceuticals Limited, Loughborough, England.

basis of reduction in corticosteroid dosages and no attempt at symptomatic assessment was made.

## MATERIAL AND METHODS

A total of 45 children were admitted to the trial. In one child the DSCG treatment had to be discontinued after a few weeks because of increasing cough and asthma in connection with the inhalations, and for this reason the child had to be excluded from further study. Thus 44 children remained in the study, half from each of the two pediatric departments in Stockholm with separate allergy units, Karolinska Sjukhuset and Sachs' Children's Hospital. Twenty-two of the children were boys and twenty-two were girls. The children selected for the trial were all over the age of 6 to ensure a good cooperation. The age range was 6-20 with an average of 13 years. The severity of the bronchial asthma in these children was such that the symptoms could be controlled only by continuous corticosteroid treatment. The drug used was prednisolone. The duration of corticosteroid treatment was between 2 and 15 years, with an average of 6 years.

All the children had for several years been seen regularly by one or the other of the two investigators and records of their daily prednisolone requirements had been kept. The principles for treatment were the same in the two hospitals. The children had been kept at the lowest possible maintenance dosage of prednisolone and all other methods of reducing their asthma had been taken, such as environmental control and full adjuvant bronchodilator therapy. Specific hyposensitization was carried out when appropriate.

Thirty children had positive skin and provocation tests. Eleven of these 30 children also had an IgE level above  $+ 2$  SD for healthy children of the same age and 19 a normal IgE level (3). Fourteen children had negative skin and provocation tests as well as a normal level of IgE.

Treatment of all 44 children with DSCG was started during October-November 1968 and continued until April 1969. Twenty-nine children were still continuing treatment in April 1970. Capsules containing a powder of 20 mg DSCG + 20 mg lactose were used for inhalation through a Spinhaler 4 times a day. The usual symptomatic treatment was kept constant during the whole trial period, with the exception of isoprenaline which was given only when necessary.

The children were examined once a month by one or the other of the two investigators and in between the monthly visits contact was kept by telephone at least once each period. Symptoms and dose of drugs used were registered daily by the parents or the patient and the diary cards were presented at each visit. During the period of the study, in common with previous years, emphasis was put on reducing the corticosteroid dosage to the lowest possible level, to maintain a reasonably good clinical condition. When possible, the dosage was

reduced by 1.25 or 2.5 mg of prednisolone (tablets of 5 mg were used) at intervals of 2 weeks or more, the size of the reduction depending on the original dosage and previous experience with the particular child. The clinical assessment of the patients' condition could also lead to an increase in dosage of prednisolone if necessary.

## RESULTS

The results were evaluated with regard to reduction in corticosteroid dosage during the period of study.

Comparisons were performed on a group basis between identical months during the trial period, November 68—April 69, and the year preceding the trial and between identical months of the two years preceding the trial.

These analyses included 42 children. Two of the 44 children had to be excluded because of incomplete information of the corticosteroid dosage during the first or second control period.

Every second month during the trial period was used for the calculations, viz. December 1968, February and April 1969. In September 1968 no child had yet been treated with DSCG. This month was included in the analysis in order to check that the starting points of the different periods did not differ considerably.

There was a significant reduction in the dosage used of corticosteroids in the group where the children were on DSCG in comparison to the year before, whereas no significant difference was found between the two control years, Table 1.

An analysis of the difference between the mean daily corticosteroid dosages during the separate months of the same period showed a gradual, small but statistically significant, drop in dosage in the group during the trial period, whereas no such reduction was attained in any of the control periods, Table 2.

It is obvious from the tables that the SD of the means is very high, thus implying a wide dosage variation between individual children.

Comparisons between mean daily corticosteroid dosage dur-

TABLE 1  
*Changes in Corticosteroid Dosages between two Control Periods 1966-1967 and 1967-1968 and between the DSCG Period 1968-1969 and the Control Period 1967-1968.*

| Month     | Number of patients | Mean average daily dosage of prednisolone (mg) |      |      |      | Results of Wilcoxon matched pairs signed ranks test |      |    |       |                |
|-----------|--------------------|------------------------------------------------|------|------|------|-----------------------------------------------------|------|----|-------|----------------|
|           |                    | Mean                                           | ± SD | Mean | ± SD | Mean diff.                                          | ± SD | N  | Z     | P (one tailed) |
|           |                    | 1966-1967                                      |      |      |      | 1967-1968                                           |      |    |       |                |
| September | 42                 | 5.85                                           | 3.96 | 6.57 | 4.34 | 0.7                                                 | 3.4  | 42 | -1.31 | 0.0951         |
| December  | 42                 | 6.11                                           | 3.17 | 6.05 | 3.83 | -0.1                                                | 3.1  | 41 | -0.37 | 0.3557         |
| February  | 42                 | 6.18                                           | 3.77 | 6.09 | 3.63 | -0.1                                                | 3.3  | 41 | -0.04 | 0.4840         |
| April     | 42                 | 7.12                                           | 5.73 | 6.64 | 4.10 | -0.5                                                | 4.5  | 42 | -0.33 | 0.3707         |
|           |                    | 1967-1968                                      |      |      |      | 1968-1969                                           |      |    |       |                |
| September | 42                 | 6.57                                           | 4.34 | 6.37 | 3.45 | -0.2                                                | 3.2  | 42 | -1.15 | 0.1251         |
| December  | 42                 | 6.05                                           | 3.83 | 5.69 | 3.87 | -0.4                                                | 4.2  | 42 | -1.66 | 0.0485         |
| February  | 42                 | 6.09                                           | 3.93 | 5.15 | 4.19 | -0.9                                                | 4.5  | 42 | -2.19 | 0.0143         |
| April     | 42                 | 6.64                                           | 4.10 | 4.99 | 3.99 | -1.7                                                | 3.1  | 42 | -3.35 | 0.0005         |

TABLE 2  
Changes in Corticosteroid Dosage between Different Months before and during DSCG Therapy.

| Year                | Number of patients | Mean average daily dosage of prednisolone (mg) |      |      |      | Results of Wilcoxon matched pairs signed ranks test |      |    |       |                |
|---------------------|--------------------|------------------------------------------------|------|------|------|-----------------------------------------------------|------|----|-------|----------------|
|                     |                    | Mean                                           | ± SD | Mean | ± SD | Mean diff.                                          | ± SD | N  | Z     | P (one tailed) |
|                     |                    | September                                      |      |      |      | December                                            |      |    |       |                |
| 1966-1967 (Control) | 42                 | 5.85                                           | 3.96 | 6.11 | 3.17 | 0.26                                                | 2.41 | 40 | -1.15 | 0.1251         |
| 1967-1968 (Control) | 42                 | 6.57                                           | 4.34 | 6.05 | 3.83 | -0.52                                               | 2.48 | 40 | -1.46 | 0.0721         |
| 1968-1969 (DSCG)    | 42                 | 6.37                                           | 3.45 | 5.69 | 3.87 | -0.67                                               | 3.10 | 42 | -1.86 | 0.0314         |
|                     |                    | September                                      |      |      |      | February                                            |      |    |       |                |
| 1966-1967 (Control) | 42                 | 5.85                                           | 3.96 | 6.18 | 3.77 | 0.33                                                | 2.49 | 42 | -1.19 | 0.1170         |
| 1967-1968 (Control) | 42                 | 6.57                                           | 4.34 | 6.09 | 3.63 | -0.48                                               | 2.44 | 42 | -0.97 | 0.1660         |
| 1968-1969 (DSCG)    | 42                 | 6.37                                           | 3.45 | 5.15 | 4.19 | -1.22                                               | 3.30 | 41 | -2.40 | 0.0082         |
|                     |                    | September                                      |      |      |      | April                                               |      |    |       |                |
| 1966-1967 (Control) | 42                 | 5.85                                           | 3.96 | 7.12 | 5.73 | 1.27                                                | 3.97 | 41 | -1.92 | 0.0274         |
| 1967-1968 (Control) | 42                 | 6.57                                           | 4.34 | 6.64 | 4.10 | 0.07                                                | 4.08 | 42 | -0.31 | 0.3783         |
| 1968-1969 (DSCG)    | 42                 | 6.37                                           | 3.45 | 4.99 | 3.99 | -1.38                                               | 3.36 | 42 | -2.82 | 0.0024         |
|                     |                    | December                                       |      |      |      | February                                            |      |    |       |                |
| 1966-1967 (Control) | 42                 | 6.11                                           | 3.17 | 6.18 | 3.77 | 0.06                                                | 2.26 | 42 | -0.27 | 0.3936         |
| 1967-1968 (Control) | 42                 | 6.05                                           | 3.83 | 6.09 | 3.63 | 0.04                                                | 2.06 | 41 | -0.10 | 0.4602         |
| 1968-1969 (DSCG)    | 42                 | 5.69                                           | 3.87 | 5.15 | 4.19 | -0.54                                               | 3.13 | 42 | -1.73 | 0.0418         |
|                     |                    | December                                       |      |      |      | April                                               |      |    |       |                |
| 1966-1967 (Control) | 42                 | 6.11                                           | 3.17 | 7.12 | 5.73 | 1.01                                                | 3.81 | 42 | -1.16 | 0.1230         |
| 1967-1968 (Control) | 42                 | 6.05                                           | 3.83 | 6.64 | 4.10 | 0.59                                                | 3.84 | 42 | -0.42 | 0.3372         |
| 1968-1969 (DSCG)    | 42                 | 5.69                                           | 3.87 | 4.99 | 3.99 | -0.71                                               | 3.49 | 42 | -1.64 | 0.0505         |
|                     |                    | February                                       |      |      |      | April                                               |      |    |       |                |
| 1966-1967 (Control) | 42                 | 6.18                                           | 3.77 | 7.12 | 5.73 | 0.94                                                | 2.96 | 39 | -1.27 | 0.1020         |
| 1967-1968 (Control) | 42                 | 6.09                                           | 3.63 | 6.64 | 4.10 | 0.55                                                | 3.86 | 42 | -0.17 | 0.4325         |
| 1968-1969 (DSCG)    | 42                 | 5.15                                           | 4.19 | 4.99 | 3.99 | -0.16                                               | 3.14 | 41 | -1.85 | 0.0322         |

TABLE 3  
*Allergy Scores in two Groups of Patients.*

| Groups                                | No. of patients whose scores are : |    |    | Total |
|---------------------------------------|------------------------------------|----|----|-------|
|                                       | 0                                  | 1  | 2  |       |
| Lower during test period than control | 3                                  | 7  | 8  | 18    |
| Equal or higher                       | 11                                 | 12 | 2  | 25    |
| Total                                 | 14                                 | 19 | 10 | 43    |

$$\chi^2 = 8.57. \quad p < 0.05.$$

0 = neg. skin test and provocation test, normal IgE level.

1 = pos. skin test and provocation test.

2 = pos. skin test and provocation test, IgE level above + 2 SD for healthy children of the same age.

ing the whole trial period of 6 months and the corresponding months during the previous year were performed for each individual (43 children with complete records both years) and the differences were tested by t-test. It was thus found that in 18 children (41 per cent) the corticosteroid dosage was significantly lower ( $p < 0.05$ ) during the trial period than during the previous year. In 3 children the dosage was signifi-

TABLE 4  
*Allergy Scores in two Groups of Patients.*

| Groups             | No. of patients whose scores are : |    |    | Total |
|--------------------|------------------------------------|----|----|-------|
|                    | 0                                  | 1  | 2  |       |
| Steroids withdrawn | 1                                  | 4  | 6  | 11    |
| Steroids continued | 13                                 | 15 | 5  | 33    |
| Total              | 14                                 | 19 | 11 | 44    |

$$\chi^2 = 8.57. \quad p < 0.05.$$

0 = neg. skin test and provocation test, normal IgE level.

1 = pos. skin test and provocation test.

2 = pos. skin test and provocation test, IgE level above + 2 SD for healthy children of the same age.

cantly higher during the trial period than during the previous year and in 22 children no significant difference between the two periods was found.

The children thus formed two groups, one of 18 who derived benefit and one of 25 who did not derive benefit. There was a significant predominance of children with evidence of allergy in the group who derived benefit in comparison to the other group, Table 3. However, no difference in duration of corticosteroid therapy or mean daily corticosteroid dosage before the trial (September 68) was found.

During the trial period of 6 months it was possible to withdraw corticosteroids completely in 8 of the 44 children.

The material was reviewed again in April 1970 when 29 children were still on DSCG therapy. One child had discontinued the treatment due to complete freedom from symptoms of asthma and 14 because of lack of interest and/or effect.

During this extended period corticosteroid therapy could be withdrawn in a further 3 children. Thus in 25 per cent of the 44 children on long term DSCG treatment it was possible to withdraw corticosteroid therapy.

Among these 11 children from whom corticosteroids were withdrawn there was a significant predominance of children with evidence of allergy in comparison to the 33 children still on corticosteroids, Table 4.

The children from whom corticosteroids were withdrawn also had a significantly lower initial corticosteroid dosage and a significantly shorter duration of corticosteroid therapy than the other group, Table 5.

#### COMMENTS

In children receiving corticosteroid treatment for bronchial asthma any symptomatic relief should lead to a reduction in corticosteroid dosage. Thus symptomatic relief can be assessed with a certain amount of objectivity by calculation of the reduction in corticosteroid dosage.

TABLE 5

*Comparison of Patients who Continued on Corticosteroids with those for whom Corticosteroids were Withdrawn.*

|                                                     | Prednisolone             |      |      |                          |      |      | P<br>(one tailed)         |
|-----------------------------------------------------|--------------------------|------|------|--------------------------|------|------|---------------------------|
|                                                     | Withdrawn                |      |      | Continued                |      |      |                           |
|                                                     | Number<br>of<br>patients | Mean | SD   | Number<br>of<br>patients | Mean | SD   | Mann<br>Withney<br>U test |
| Duration of<br>prednisolone<br>therapy<br>in years  | 11                       | 4.73 | 2.37 | 33                       | 6.76 | 3.50 | 0.0436                    |
| Prednisolone<br>dosage<br>(Sept. 1968)<br>in mg/day | 11                       | 3.68 | 1.73 | 33                       | 7.24 | 3.33 | < 0.0007                  |

By using this method of assessing the effect of DSCG we found a significant reduction of the corticosteroid dosage in the group of children during a 6 months' period of treatment with DSCG in comparison to the same period the preceding year thus implying a positive effect due to the treatment.

However, this overall reduction of dosage in the group is due only to some of the children being improved. There is a wide variation between the individuals. Eighteen children (41 per cent) are responsible for the overall reduction of the corticosteroid dosage whereas in 25 children (59 per cent) no effect could be shown.

The figures for complete withdrawal of corticosteroids, 18 per cent, within 6 months and 25 per cent within 18 months of treatment with DSCG are considerably lower than the 61 per cent withdrawal of corticosteroids within 3 months described by Morrison Smith and Devey (9). However, the materials are not quite comparable. The average duration of corticosteroid treatment in our children was 6 years and in no child was the duration less than two years, whereas in their children the average duration was 2½ years. Further-

more they did not state whether the corticosteroid dosage at the start of the trial was the minimal effective dose as in the present study. Both are facts which might have an influence upon the differences in results. The possibility that the Isoprenaline added to the DSCG in their trial had a bearing upon the results must also be considered.

Two criteria seem to have a bearing upon our results, viz. proved allergic origin of the asthma and comparatively low corticosteroid dosage during a shorter period of time before the start of the trial.

The predominance of asthma with evidence of allergy in the children who derived benefit from the treatment with DSCG is in conformity with the hypothesis of the action of the drug as well as with the impression of other clinicians that the best effect is obtained in patients with allergic asthma (1, 6).

The higher the corticosteroid dosage a child is given and the longer the duration of such therapy the more depressed will the adrenocortical function of the patient be (2, 7, 8). This is one of the reasons for the difficulties in withdrawing corticosteroid therapy in general. A mean daily dose of 5 mg prednisolone for two years or more invariably suppresses the adrenocortical function of children (2), a fact that must be considered when judging the effect of DSCG in this particular group, in which the larger group of 33 children with continued corticosteroid treatment had an initial mean daily dose of 7.24 mg prednisolone and a mean duration of corticosteroid therapy of more than 6 years.

In view of the apparent severity of the disease in the children studied and of the probable depressed adrenocortical function in the majority, a reduction of the steroid dosage in 41 per cent within 6 months and a complete withdrawal of corticosteroids in 25 per cent within 1½ years must be regarded as favourable.

However, it must be stressed that disodium cromoglycate can not be expected to exert any remarkable effect in corticosteroid reduction except in children with allergen induced

asthma and with a comparatively well maintained adrenocortical function.

### SUMMARY

Fourty-four children with perennial bronchial asthma requiring long term corticosteroid treatment were treated with DSCG for a minimum of 6 months and a maximum of 18 months. The corticosteroid dosages were significantly reduced in 18 of the children during the first 6 months of the trial in comparison to the previous year and completely withdrawn in 8 children during the same period. During prolonged treatment up to 18 months, corticosteroids were withdrawn in a further 3 children. In all, 25 per cent of the children managed without corticosteroids after 18 months of treatment with DSCG. The children who obtained benefit from treatment with DSCG were those with allergic asthma, who had been on a comparatively low corticosteroid dosage for a shorter period of time.

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