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Nebulised cromoglycate, theophylline, and placebo in preschool asthmatic children

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SUMMARY Sixteen children aged under 5 years with chronic asthma completed a double-blind crossover trial of treatment with oral choline theophyllinate (6.7 mg/kg four times daily) and nebulised sodium cromoglycate (20 mg four times daily). The trial comprised three 8-week treatment periods during which active sodium cromoglycate, active choline theophyllinate, and placebo were given in random order. Symptom scores for sleep disturbance, cough, wheeze, and daily activities were similar during the three treatment periods if results were analysed using Friedman's non-parametric analysis of variance. However the Mantel-Haenszel test showed that sodium cromoglycate was superior to placebo ($P < 0.05$) in maintaining normal daily activities. Either regimen is safe and well tolerated by young children.

Sodium cromoglycate (SCG) and oral theophylline have been shown to be of value in the long-term management of asthma in childhood.¹⁻³ In a collaborative study in children aged over 5 years both drugs were shown to be equally effective.⁴ However, there have been few long-term studies in young preschool asthmatic children of drugs known to be effective in controlling symptoms in older children or adults. In such an age group, nebulised SCG was shown to be superior to placebo.⁵ Choline theophyllinate (CT) is a widely used theophylline preparation in young asthmatic children and we know of no long-term controlled study confirming its efficacy. We set out to compare the relative usefulness of oral CT and nebulised SCG in a group of preschool asthmatic children who were unable to use the spinhaler effectively.

Patients

Sixteen patients, 11 boys and 5 girls, took part in the study. Their ages ranged from 1 year 9 months to 4 years 5 months (mean 3 years 5 months). All were within $\pm$ one standard deviation of the mean predicted for age for height and weight on standard centile charts.⁶ Fifteen gave a personal or family history of associated atopic disorders. Ten children suffered from eczema, 6 from recurrent rhinitis, and 2 from urticaria. Symptoms had started in the first year of life in 4 and during the second year in a further 8. Wheezing attacks were precipitated by upper respiratory tract infections in 15, by exercise in 11, and by specific allergens in 5. Of 11 children in whom skin tests were performed, 7 had multiple positive reactions to common antigens—such as house dust mite, pollens, and animal dander.

For the group there had been 39 hospital admissions in the year preceding the trial, a range of 1-5 (median 2) admissions per child. Fifteen children had received systemic treatment with steroids previously, but none was on maintenance steroids. The control of asthma was poor on routine treatment and all had had at least 2 wheezing episodes during the 6 weeks preceding the trial. Treatment regimens were intermittent or regular salbutamol (in 7), salbutamol combined with CT (in 6), a theophylline preparation alone (in 2), and regular orciprenaline (in 1). Five of the patients on oral salbutamol had salbutamol respirator solution 0.5% available at home for use by an air pump nebuliser unit as required (2.5 mg 3-4 hourly).

Methods

A double-blind crossover trial was carried out comprising three 8-week treatment periods during

which active SCG, active CT, and placebo were given in random order. Both drugs were given 4 times daily—SCG 20 mg diluted in 2 ml sterile water, administered via a Pari pump and nebuliser unit over a period of 5 minutes, or CT syrup orally in a dose of 6–8 mg/kg per dose (mean 6.7, about 4 mg/kg theophylline). Theophylline doses were not individualised but random non-timed capillary blood samples were taken by an independent observer during periods of active CT treatment; the main investigators were not told the sampling times. In addition to trial drugs, patients were supplied with salbutamol respirator solution 0.5% to be given by nebuliser in a dosage of 2.5 mg in 2 ml sterile water every 3 hours as necessary for wheeze. Nebulised salbutamol dosage and any additional treatment with drugs prescribed by family doctors were also recorded. During the baseline period before the trial parental co-operation was assessed and parents were instructed in the use of nebulisers and the completion of diary score cards.

Response to treatment was assessed using diary cards recording scores on a 0–3 scale of increasing severity for the following symptoms: night disturbance, cough, wheeze, and daytime activity. It proved exceedingly difficult to obtain reliable measurements of peak flow rates in most of our young patients and this index of severity was excluded from the final analysis. Additional treatment with bronchodilators was noted, and significant events such as intercurrent illnesses, short-term courses of corticosteroids, and admissions to hospital.

Patients were assessed clinically at the start of the study and 4-weekly thereafter. At the end of each 8-week treatment period an opinion on the efficacy of treatment during that time was obtained from parents. Parental preference was stated finally at the end of the trial.

Analytical methods. Diary card scores were analysed by two separate statistical methods. For each analysis the first 2 weeks of an 8-week treatment period were disregarded to eliminate crossover effects of drugs. Friedman's non-parametric analysis of variance was used to compare symptom scores for the three treatment periods. Individual symptoms were also analysed separately. The Mantel-Haenszel test⁷ was applied to the data with pair wise comparison of placebo and drugs for each of the 4 main symptoms. Two scoring systems were used, the simple scoring method which allocated values from 0 to 3 for each symptom, and the Rank scoring method (the former gives greater weight to differences between mild symptoms). Underlying the statistical approach, two assumptions were made which are manifestly

incorrect. These were that each day's symptoms were independent of the next, and that the patients were a homogeneous sample.

Results

The results for children completing the trial are shown in Tables 1 and 2. No significant difference in bronchodilator dosage occurred during the three treatment periods. Three of the 16 children in the trial were admitted to hospital and 2 were treated with corticosteroids. SCG was the treatment most often preferred by parents, but this was not statistically significant.

Examination of the two test statistics, the Friedman in Table 1 and the Mantel-Haenszel in Table 2, shows broad agreement. The Friedman test produces no significant differences between the three treatments; the Mantel-Haenszel procedure identifies a significant difference between SCG and placebo with respect to activity ($P < 0.05$). This difference

Table 1 Comparison of nebulised sodium cromoglycate and oral choline theophyllinate

Mean weekly scores (weeks 3–8)	Sodium cromoglycate	Choline theophylline	Placebo	Friedman statistic
Sleep	2.10	1.50	1.92	2.82 NS
Cough	3.44	3.02	3.96	0.25 NS
Wheeze	2.35	2.26	2.21	0.96 NS
Activity	1.45	1.31	2.10	0.68 NS
Bronchodilator usage/1 week	1.71	1.43	1.38	0.25 NS
No of hospital admissions	—	1	2	—
Courses of steroids	—	—	2	—
Parental preference	7	2	4	—

Table 2 Analysis of symptoms*

	Rank scores		Simple scores	
	Mantel-Haenszel statistic	P	Mantel-Haenszel statistic	P
Sleep disturbance				
P v CT	0.37	NS	0.61	NS
P v SCG	0.52	NS	0.98	NS
CT v SCG	1.53	NS	2.14	NS
Cough				
P v CT	0.12	NS	0.01	NS
P v SCG	0.63	NS	0.05	NS
CT v SCG	1.06	NS	0.61	NS
Wheeze				
P v CT	1.04	NS	0.04	NS
P v SCG	1.10	NS	0.32	NS
CT v SCG	0.20	NS	0.15	NS
Activity				
P v CT	3.00	NS	2.21	NS
P v SCG	6.42	<0.05	4.29	<0.05
CT v SCG	0.42	NS	0.75	NS

*Statistical outliers excluded.

could occur because the Mantel-Haenszel test is a more powerful statistical tool. Stevens rejects the Mantel-Haenszel in favour of the Friedman test for reasons quoted previously, namely lack of independence and homogeneity (M T Stevens, 1980, personal communication). However, if independence is not assumed, the Friedman test must also be rejected. A necessary condition in a clinical trial for the Mantel-Haenszel test is patient homogeneity. With respect both to cough and activity on placebo treatment, one child was identified as a statistical outlier. Another outlier was identified on placebo with respect to sleep disturbance symptoms. On rejecting these children, standard tests showed the sample homogeneous and the Mantel-Haenszel test was applied to the smaller sample (Table 2). When the Mantel-Haenszel statistic was calculated for all 16 in the trial, the overall results are greatly changed. SCG and CT then differ from placebo in their effect on general activity ($P < 0.01$) for both Rank and simple score methods. Moreover, both drugs were also superior to placebo in the control of cough ($P < 0.01$) and CT superior to placebo in minimising sleep disturbance ($P < 0.05$ for Rank method and simple scores). Neither drug was significantly different from the other or from placebo in the control of wheeze.

In general, the drugs were well tolerated. During the active CT period, 1 child was irritable and another had intermittent vomiting at a time when serum theophylline concentration was within the therapeutic range (10–20 $\mu\text{g/ml}$ (55–110 $\mu\text{mol/l}$)). Random measurements of serum theophylline confirmed that all children received theophylline during the active treatment period. Although no effort was made to individualise dosage, of levels obtained 2–6 hours after administration, 50% were between 10 and 20 $\mu\text{g/ml}$ (55 and 110 $\mu\text{mol/l}$) and only 20% were lower than 5 $\mu\text{g/ml}$ (28 $\mu\text{mol/l}$).

Discussion

This study shows that neither SCG nor CT is strikingly different from placebo in controlling symptoms in preschool asthmatic children, although SCG was superior to placebo in maintaining normal daily activities. The inclusion of 2 patients shown to be statistical outliers in the Mantel-Haenszel analysis produces the result showing SCG and CT to be superior to placebo in most respects apart from the control of wheeze. Although the inclusion of outliers in the analysis is statistically incorrect, the possibility exists that an enhanced response to treatment contributed to the statistical rejection of these 2 patients. This finding would have been in general agreement with a collaborative study of

these agents in older children.⁴ The dose schedules for both drugs may have been less than optimal. The mean CT dosage of 6.7 mg/kg four times daily is equivalent to a mean theophylline dosage of about 4 mg/kg four times daily, which is lower than the high dose theophylline regimen currently recommended.⁸ In the absence of strict monitoring of serum theophylline concentration, we felt that the risk of toxicity with a higher theophylline dose (6 mg/kg four times daily) was not acceptable. It is likely also that the dose of cromoglycate administered was less than intended. Careful weighing of the nebuliser unit before and after nebulising 2 ml cromoglycate solution showed that on average 0.8 ml remained in the nebuliser after apparent complete emptying. This was true also for 5 other commercially available nebuliser units.

A pronounced decrease in symptoms and hospital admissions was noted throughout the trial period, suggesting a strong placebo effect. In general, low symptom scores were recorded throughout the trial period and thus there was little improvement that any treatment could be expected to achieve. However, both drug preparations were superior to placebo in maintaining normal daytime activities when all patients were analysed by the Mantel-Haenszel statistic, but only SCG was superior when the statistical outlier was excluded. Parental assessment of a child's daytime activity is of course subjective and difficult to quantify. In comparing the relative merits of SCG by nebuliser and oral CT, the simplicity of administering oral CT has to be balanced with the need for regular monitoring of serum theophylline concentration if a higher dose regimen is used, as well as the palatability of CT or related theophylline preparations. We found that children tolerated nebulised cromoglycate extremely well, but the inconvenience of using nebuliser units four times daily must also be considered. These units were available to all of our patients for the administration of nebulised salbutamol, a practice we have continued since the completion of the trial. Thus, any added cost factor applies whatever the drug regimen chosen. When CT is used routinely for controlling symptoms of chronic asthma, the daily dosage must be taken into account when assessing how much additional theophylline can be given safely when such children are admitted to hospital with acute exacerbations of asthma. Ideally, laboratory facilities for monitoring theophylline levels should be available in centres treating such patients.

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Testicular complications in connective tissue disease

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SUMMARY Acute testicular symptoms are described in 2 patients with Schönlein-Henoch syndrome and in 1 with juvenile rheumatoid arthritis. The literature on testicular involvement in connective tissue disease of childhood is reviewed.

Testicular vasculitis in Schönlein-Henoch syndrome is mentioned in only one current general paediatric textbook.¹ None the less, the phenomenon is well known, and Sahn and Schwartz² reported the finding in 5 of a series of 20 patients, 13 of whom were boys. Two more cases are here described, together with what is, as far as I can establish, the first recorded case of testicular involvement in juvenile rheumatoid arthritis.

Patients

Case 1. A 7-year-old boy was admitted with acute left scrotal pain and swelling. He had had an upper respiratory tract infection during the previous week but there were no other symptoms. Exploration showed the testis and epididymis to be swollen and congested but there was no torsion. Postoperatively, he developed swelling of his right wrist and an extensive urticarial rash on the backs of his legs, thighs, and buttocks. Schönlein-Henoch syndrome was diagnosed.

Investigative findings

Erythrocyte sedimentation rate (ESR) was 52 mm/1st hour. Urine analysis showed a trace of albumin

and a few red cells. The following investigations were normal or negative: full blood count, stool examination for occult blood, antistreptolysin O titre (O-AST), tests for LE cells, antinuclear and anti-DNA antibodies, and rheumatoid factor. He was treated with paracetamol and made a good recovery within a week.

Case 2. A 7½-year-old boy was referred with a 3-week history of abdominal cramps, vomiting, diarrhoea, and a rash. He had developed painful swelling of both ankles 48 hours before admission. On examination he had an extensive haemorrhagic-urticarial rash over his lower limbs, including the buttocks, and on the forearms. Both feet were oedematous and there was painful swelling of both ankle joints.

Investigative findings

Urine analysis showed large numbers of red cells and some cellular casts. Stools were strongly positive for occult blood. The following investigations were normal or negative: full blood count, ESR, clotting studies, O-AST, serum complement, tests for LE cells, antinuclear antibodies, rheumatoid factor, blood urea, creatinine, and electrolyte levels.

Schönlein-Henoch syndrome was diagnosed and, because of the severity and duration of his abdominal pain, he was started on prednisolone 10 mg, three times a day. His condition improved on this regimen but, on the 7th day in hospital, he developed acute