Duration of action of sodium cromoglycate on exercise induced asthma: comparison of 2 formulations

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SUMMARY Thirteen asthmatic children aged 9-14 years participated in a double blind randomised trial to compare the effectiveness and duration of action of 2 formulations of sodium cromoglycate; one a 20 mg capsule of powdered sodium cromoglycate delivered by turbo inhaler (spinhaler), and the other 1 mg of aerosolised sodium cromoglycate delivered by pressurised cannister inhaler (aerosol). The children performed exercise tests on each of 3 days in a 10 day period—15 minutes, 2 hours, and 6 hours after inhalation of powder, aerosol, or a placebo. Two patients were not protected from exercise induced asthma by either formulation of sodium cromoglycate. Among the remaining patients both formulations gave good protection from exercise induced asthma 15 minutes after inhalation, and the effect of both wore off steadily over the next 6 hours. The spinhaler gave appreciably better protection than the aerosol at 15 minutes after inhalation, and was the only formulation to provide good protection at 2 hours and 6 hours. The more limited effectiveness of the aerosol may be explained by the lower dose of sodium cromoglycate and the more complicated inhalation technique required.

The drug sodium cromoglycate (SCG) is known to protect most asthmatic children against clinical, antigen induced, and exercise induced asthma (EIA)¹⁻³ and the duration of this protection has been shown to last up to 6 hours or more.^{4,5} A new formulation of SCG has been introduced comprising 1 mg aerosolised SCG delivered by a pressurised cannister inhaler (aerosol). We compared the protective effect and the duration of action of this formulation with that of the original formulation of 20 mg powdered SCG delivered by turbo inhaler (spinhaler).^{6,7}

Patients and methods

Thirteen asthmatic children aged 9-14 years participated in the double blind randomised trial and their anthropometric data and usual treatment are presented in Table 1. They attended the Pulmonary function laboratory on 3 occasions over 10 days. On each occasion they inhaled 1 of 3 preparations; CSG aerosol, CSG spinhaler, or placebo and then performed 3 identical exercise tests 15 minutes, 2 hours and 6 hours afterwards. One patient performed only 1 exercise test on each day 15 minutes after drug inhalation and 2 patients performed only the 15 minute and 6 hour tests. Their results have been included where appropriate. In addition, 5 of

13 patients performed an exercise test 4 hours after treatment. Two placebos were used, one identical in format to the spinhaler and the other to the aerosol. The patients inhaled both a spinhaler and an aerosol before the first exercise test, one an active preparation and the other a placebo, except on the placebo day when both preparations were placebos.

The exercise consisted of 6 minutes of cycling on a cycle ergometer (Lode Inst, N V) at a fixed load in such a manner as to achieve 60% of maximum predicted oxygen consumption.⁸ Once set this load was kept constant throughout the study for each

Table 1 *Details of patients*

Case No	Sex	Age (yr)	Height (cm)	Weight (kg)	Usual treatment
1	M	11	139	31	ISB
2	F	9	136	33	ISB
3	M	9	138	30	ISB
4	F	12	152	46	ISB
5	M	10	137	30	ISB, HDT
6	M	12	145	30	ISB
7	F	13	147	41	ISB, HDT
8	M	12	140	32	ISB
9	F	14	151	39	ISB
10	M	12	135	27	ISB
11	M	13	149	30	ISB, SCG
12	M	12	147	40	ISB
13	M	14	145	35	ISB, ICS

ISB = intermittent sympathomimetic bronchodilator; HDT = high dose theophylline; SCG = sodium cromoglycate; ICS = inhaled corticosteroid.

individual. To keep all exercise tests identical the patients breathed cold (6.6°C) and dry air from a specially designed respiratory circuit. These respired air conditions were kept constant for all tests. The patient was connected to the system and breathed this gas for 5 minutes before starting the exercise, throughout the exercise period, and afterwards until his or her forced expiratory volume (FEV) in 1 s had passed the minimum value and returned to within $\pm 10\%$ of the pre-exercise value.

Lung function tests were performed in triplicate and the best effort was chosen from each set. The FEV_1 was measured with an electronic spirometer (Hewlett-Packard model 4730A). Measurements were made before treatment was given, at 15 minutes, (that is just before beginning the first exercise run), and at intervals after the completion of exercise. The same protocol was followed during the next 3 or 4 exercise tests performed each day. All measurements were performed with the patients seated on the cycle ergometer. The severity of EIA was calculated as the maximum percentage fall in FEV_1 after exercise ($\Delta\text{FEV}_1(\%)$):

$$\Delta\text{FEV}_1(\%) = \frac{\text{pre-exercise FEV}_1 - \text{minimum post-exercise FEV}_1}{\text{pre-exercise FEV}_1} \times 100$$

Table 2 Individual baseline forced expiratory volume values before exercise and after the 3 treatments

No Case	15 min	2 hr	4 hr	6 hr	Mean	% of predicted normal
1	1.67	1.56		1.60	1.61	78
2	1.60	1.65		1.50	1.58	93
3	1.64	1.50		1.60	1.58	81
4	2.15	2.12		1.74	2.01	84
5	1.70	1.69		1.42	1.55	81
6	2.18	2.09		2.06	2.11	89
7	2.32	2.34		2.33	2.32	98
8	1.57				1.57	74
9	2.03	2.06	2.08	2.00	2.05	82
10	1.36	1.42	1.41	1.40	1.40	69
11	1.76	1.78	1.76	1.78	1.78	67
12	1.85	1.78	1.87	1.81	1.84	74
13	1.69	1.98	1.95	1.89	1.89	77
Mean	1.81	1.83	1.81	1.76	1.79	80.5
SEM	0.08	0.08	0.11	0.08	0.08	2.5

Table 3 Mean value (SEM) of various exercise parameters after inhalation of sp inhaler, placebo, and aerosol

	Sp inhaler				Placebo				Aerosol			
	15 min	2 hr	4 hr	6 hr	15 min	2 hr	4 hr	6 hr	15 min	2 hr	4 hr	6 hr
Ventilation (l/minute)	47.0 (3.4)	44.0 (2.7)	43.0 (3.6)	43.0 (3.4)	49.0 (2.6)	45.0 (2.5)	48.0 (6.6)	47.0 (2.7)	46.0 (2.1)	50.0 (3.6)	47.0 (4.8)	46.0 (3.9)
Oxygen consumption (ml/minute)	1205 (85.2)	1205 (85.6)	1272 (104.3)	1193 (82)	1263 (56.4)	1257 (102)	1282 (116)	1310 (107)	1265 (87)	1331 (86)	1429 (155.5)	1384 (115.4)
Heart rate (per minute)	174 (6.0)	180 (4.0)	178 (5.0)	168 (5.0)	173 (5.0)	174 (5.0)	179 (4.0)	177 (3.0)	174 (3.0)	176 (5.0)	174 (3.0)	171 (4.0)

where the pre-exercise value was that measured immediately before starting exercise while breathing the test gas.

Statistical comparisons were made between either drug and placebo or drug and drug tests by means of student's paired t test and the SEM given in the text refers to these comparisons. One way analysis of variance⁹ was used to compare baseline lung function between different types of test, and differences were considered significant where $P < 0.05$.

Results

Table 2 gives individual baseline FEV_1 values for each exercise test after each of the 3 treatments and the mean values of the various exercise parameters are in Table 3. There were no significant differences between any of these parameters in the tests.

The $\Delta\text{FEV}_1(\%)$ for each patient in each of the tests is given for each treatment (Table 4). EIA was significantly attenuated at 15 minutes after pre-exercise treatment with either aerosol or sp inhaler compared with placebo (ΔFEV_1 , mean (SEM) = 17 (2%) (aerosol), 12 (4%) (sp inhaler), and 25 (4%) (placebo); $P < 0.05$ for each drug compared with placebo). Only the sp inhaler treatment was still effective after 2 hours in protecting the patients against EIA. Analysis of the data available on the 5 patients who exercised 4 hours after treatment is limited because of the small group size. When exercise was performed 6 hours after treatment there was no appreciable protection by the aerosol but the sp inhaler treatment gave a significantly better protection than either aerosol or placebo ($\Delta\text{FEV}_1\%$, mean (SD) = 24 (5), 33 (3), and 31 (5); $P < 0.05$ for each comparison).

Two of the patients (cases 1 and 9) were not protected in any test by either formulation of SCG and indeed the patient in case 9 suffered greater EIA after the drug than after the placebo. Since these 2 patients were unprotected their results could not be used to evaluate the duration of protection in the majority group of 11 patients. The results were therefore recalculated for these 11 patients alone and are summarised in the Figure. There were 11 studies

Table 4 Individual postexercise falls in forced expiratory volume (%) after placebo (P), aerosol (A), and spinhaler (S)

Case No	15 min			2 hr			4 hr			6 hr		
	P	A	S	P	A	S	P	A	S	P	A	S
1	19	17	58	—	—	—	—	—	—	29	47	31
2	4	12	0	—	—	—	—	—	—	13	34	5
3	14	20	1	5	48	8	—	—	—	24	45	15
4	17	4	8	16	9	0	—	—	—	22	19	7
5	40	13	5	52	23	11	—	—	—	50	39	63
6	27	9	2	21	26	19	—	—	—	50	36	40
7	37	5	6	34	3	0	—	—	—	34	21	13
8	33	24	10	—	—	—	—	—	—	—	—	—
9	9	23	13	7	30	40	5	26	9	5	33	12
10	36	27	7	46	35	33	52	31	35	73	51	48
11	22	26	25	28	10	4	21	20	12	21	18	6
12	51	22	15	22	12	22	37	32	18	25	24	27
13	20	14	7	21	19	13	20	17	29	25	23	19
Mean	25	17	12	15	21	12	27	25	21	31	33	24
SEM	4	2	4	5	4	3	8	3	5	5	3	5

Figure Mean (SE) postexercise fall in forced expiratory volume (FEV) expressed as per cent baseline in the placebo and drug studies for the 11 subjects protected by sodium cromoglycate. The number of patients tested at each time after the medication is given.

at 15 minutes, 9 at 2 hours, and 10 at 6 hours. As there were only 4 studies at 4 hours these have been omitted. Analysis in the protected group showed appreciably less EIA at all 3 times after inhalation for the spinhaler compared with placebo but only at the 15 minute test for the aerosol. As can be seen from the Figure, the protection given by the spinhaler was greater than that by the aerosol at all times, but the difference between them was significant only at 15 minutes and 2 hours and protection wore off steadily over the 6 hour period.

Discussion

This controlled study aimed at comparing the relative effectiveness and duration of action of 2

formulations of SCG and a placebo. The results showed that both formulations were effective in protecting most young asthmatics from EIA when given just before exercise. These results agree with those of Silverman and Andrea³ and of Anderson *et al.*⁴ in their investigation of the SCG spinhaler formulation. The results further indicated that protection can last up to 6 hours and that in most patients the spinhaler was more effective than the aerosol treatment. SCG in powder form has already been shown to have a similar duration of action in protecting against EIA⁴ and against allergen challenge.⁵

The method for evaluating the effectiveness and duration of the 3 treatments was that of serial exercise tests at intervals after inhalation as described by Silverman *et al.*¹⁰ The mean baseline pre-exercise FEV₁ values were 80% of that predicted for the whole group and there were no appreciable differences in baseline lung function between either the individual drug formulations or between the individual time intervals that could have biased the results. In the light of new findings on the relative importance of airway cooling by respiratory heat loss¹¹ we added the regulation of inspired air conditions to the method of Silverman *et al.*¹⁰

The aerosol formulation of SCG has already been proved an effective preventive drug both clinically and in laboratory studies.^{6,7} The only study of its protection against EIA¹² was performed while the patients exercised immediately after drug administration, and it compared only the effect of the new formulation to that of placebo. We know of no published reports that compare the protection and duration of action of the new formulation of SCG to that of the powdered spinhaler preparation in EIA. Although the somewhat better protection of the spinhaler treatment may be because the dose used

was 10 times that of the aerosol formulation, this difference is probably an overestimate since only a small proportion of the powder is in particles small enough to penetrate the airways.¹³

We believe that our results show that both formulations of SCG can protect children against EIA if taken shortly before exercise. The subsequent better duration of protection by the older spinhaler formulation is probably due to the simpler inhalation technique, which is more suitable for children or patients who have not perfected the technique for inhaling a pressure packed aerosol.

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