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Comparison of nedocromil sodium and sodium cromoglycate administered by pressurized aerosol, with and without a spacer device in exercise-induced asthma in children

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ABSTRACT: To compare the effectiveness of nedocromil sodium (NS) and sodium cromoglycate (SCG) administered by metered dose inhaler (MDI) in preventing exercise-induced asthma (EIA), 12 asthmatic children with EIA were studied in a randomized, double-blind, cross-over, placebo-controlled study.

NS and SCG were given by MDI alone, and by MDI with a 700 ml spacer device (Fisonair, Fisons, UK), in order to assess the benefit of using such a device. Following a baseline exercise challenge, the protective effect of NS, SCG or placebo was evaluated in each subject. The percentage fall in forced expiratory volume in one second, and percentage protection were measured.

NS and SCG provided a significant and comparable protection from EIA, and both were better than placebo. No further improvement was observed after drug administration *via* the spacer.

Both NS and SCG are effective in preventing EIA in children, when administered at the recommended clinical dose, and the use of a spacer for administering the drug provides no advantage if the technique of inhalation is good.

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Sodium cromoglycate (SCG) and nedocromil sodium (NS) are two prophylactic drugs for asthma, which are also effective in preventing exercise-induced asthma (EIA) both in adults and in children [1–4].

Because of its additional activity on mucosal mast cells, NS could be viewed as more effective than SCG in preventing EIA [5, 6]. The limited amount of data available at present on such comparisons is not consistent [7–9]. Moreover, it is not known whether the use of spacer devices, which are widely prescribed for administration of $beta_2$-agonists and corticosteroids from a metered dose inhaler (MDI) in children, could also be advantageous for administration of NS and SCG.

To compare the effectiveness of NS and SCG in preventing EIA in childhood, and to assess whether the use of a large volume spacer could be useful, a group of children with asthma and EIA was investigated in a double-blind, cross-over, placebo-controlled study.

Patients

Twelve children (7 males, 5 females), mean age 11 yrs (range 6.5–13.5 yrs) with asthma as defined by the American Thoracic Society [10], were studied. They had been admitted to the Istituto Pio XII of Misurina (Belluno) in the Italian Alps (1,756 m above sea level) for at least three months before the study. All of the children had a positive skin prick test response to one or more of the most common allergens (*Dermatophagoides pteronyssinus, D. farinae,* grass pollen, *Parietaria*). They were known to have EIA, with a fall in forced expiratory volume in one second (FEV_1) >15% after exercise test on a treadmill, and they were on inhaled medication only.

Equipment

Pulmonary function was assessed with a Vitalograph compact spirometer (Vitalograph, Buckingham, UK). MDIs containing NS, SCG or placebo (propellant only) were supplied by Fisons plc, Pharmaceutical Division, Loughborough, UK. A spacer device developed by Fisons plc (Fisonair) was used. Fisonair is characterized by a universal socket, a 700 ml conical chamber, and a valve mechanism, which is extremely light and operates at very low inspiratory flow rates.

Methods

Design of the study

Because of the prolonged stay at altitude, patients were able to withdraw from their inhaled steroids and SCG at

least one week before the study [11]. $Beta_2$-agonists were allowed up to 12 h beforehand.

Exercise tests were performed on separate days, at the same time of each of the seven study days. Each patient completed the study within 10 days. The exercise challenge consisted of 6 min of running on a treadmill, with a 10% slope and the speed adjusted to give an increase in heart rate to 180 beats·min^{-1}. Pulmonary function was assessed at the end, one minute after the end, and thereafter at 5 min intervals for 30 min after challenge. The ambient temperature ranged between 22–25°C, and the relative humidity between 35–45% on the different study days.

NS 4 mg, SCG 10 mg, or placebo were administered, according to a randomized, double-blind, cross-over design. Each drug was inhaled in two puffs, either directly from an MDI or *via* the Fisonair (immediately after the actuation of MDI), with the technique always supervised by the same physician (A.C.). On the first day of the study, the degree of EIA in each subject was assessed with a baseline exercise challenge. On the following days, pulmonary function readings were taken immediately before, and 30 min after, drug administration (pre-exercise value), and then the exercise test was performed. Results were expressed as percentage fall in FEV_1 (% fall FEV_1), where:

$$\%\ \text{fall } FEV_1 = \frac{\text{pre-exercise } FEV_1 - \text{lowest } FEV_1 \text{ after exercise}}{\text{pre-exercise } FEV_1} \times 100$$

Protection from EIA provided by each treatment was calculated as follows:

$$\%\ \text{protection} = \frac{Pc - Pt}{Pc} \times 100$$

where Pc is the baseline % fall FEV_1 and Pt is the % fall FEV_1 after each treatment.

The patients' parents gave informed consent and the protocol was approved by the Hospital Ethics Committee.

Statistical analysis

Analysis of variance for repeated measures and paired Student's t-test (corrected by Bonferroni's t-test when appropriate) were used for analysis of data. Differences were considered significant if $p<0.05$.

Results

Mean FEV_1 values on different study days were statistically comparable and no change of mean FEV_1 was observed 30 min after administration of each one of the three formulations (table 1).

Results for % fall FEV_1 observed after baseline exercise test performed on the first day of the study, and after treatment with NS, SCG or placebo, administered from the MDI with or without Fisonair, are detailed in table 2. A significant decrease in mean % fall FEV_1 with respect to baseline exercise test was observed after treatment with NS and SCG but not with placebo (analysis of variance: $p<0.001$; Student's t-test: baseline *versus*: i) NS, $p<0.005$; ii) SCG, $p<0.005$; and iii) placebo, p=nonsignificant). The decrease of % fall FEV_1 obtained with NS or SCG was comparable (Student's t-test: p=nonsignificant) and both were significantly better than placebo ($p<0.005$). No difference was observed when drugs were administered with or without the Fisonair (Student's t-test: MDI *versus* Fisonair p= nonsignificant with all the formulations). The percentage protection from EIA obtained in each subject after treatment with NS, SCG or placebo is presented in Table 3. Both NS and SCG provided a mean percentage of protection greater than 50% regardless of the device used. A protection value greater than 50% was obtained in eight patients (nine with the spacer) treated with NS, in nine (nine with the spacer) treated with SCG, and in one (three with the spacer) who received placebo.

Table 1. – FEV_1 (*l*) in 12 asthmatic children under baseline condition, and before and after treatment with nedocromil sodium (NS), sodium cromoglycate (SCG) or placebo, administered with a metered dose inhaler (MDI) without or with the spacer (Fisonair)

	Baseline	NS		SCG		Placebo	
		MDI	Spacer	MDI	Spacer	MDI	Spacer
Pretreatment							
Mean	1.94	1.95	2.01	2.01	1.99	2.05	2.07
SD	0.40	0.46	0.48	0.46	0.45	0.48	0.44
Post treatment							
Mean	-	2.00	2.03	2.01	2.00	2.04	2.09
SD	-	0.45	0.47	0.43	0.48	0.45	0.48

Mean (SD) predicted FEV_1 value: 2.19±0.53 *l*. FEV_1: forced expiratory volume in one second.

Table 2. – Percentage fall in FEV_1 in 12 asthmatic children, after baseline exercise test and after treatment with nedocromil sodium (NS), sodium cromoglycate (SCG) or placebo administered with a metered dose inhaler (MDI) without or with the spacer (Fisonair).

Pt	Baseline	NS		SCG		Placebo	
no.		MDI	Spacer	MDI	Spacer	MDI	Spacer
1	54.3	40.4	16.0	24.4	27.3	57.1	62.7
2	55.3	5.8	3.3	5.9	4.9	29.9	18.8
3	27.6	5.0	7.2	14.0	19.0	15.1	22.5
4	49.3	21.9	19.8	10.5	23.2	52.8	46.3
5	28.2	6.3	8.1	7.8	9.6	12.2	11.3
6	29.8	7.4	8.1	9.6	8.0	32.2	25.9
7	19.2	11.2	12.3	18.1	9.5	25.1	22.9
8	18.7	9.3	11.8	10.1	10.0	14.9	15.6
9	27.8	30.0	18.9	11.5	11.0	25.9	27.7
10	53.3	27.1	20.2	24.8	21.2	51.0	45.0
11	36.2	3.0	2.6	0.0	4.1	27.9	14.5
12	34.5	6.6	6.6	4.7	4.6	31.7	37.9
Mean	36.2	14.5	11.6	11.8	12.7	31.3	29.3
SD	13.5	12.2	6.3	7.5	7.9	15.1	15.6

FEV_1: forced expiratory volume in one second.

Table 3. – Percentage of protection from exercise-induced asthma in 12 asthmatic children after treatment with nedocromil sodium (NS), sodium cromoglycate (SCG) or placebo administered with a metered dose inhaler (MDI) without or with the spacer (Fisonair)

Pt	NS		SCG		Placebo	
no.	MDI	Spacer	MDI	Spacer	MDI	Spacer
1	25.6	70.5	55.1	49.7	-5.1	-15.5
2	89.5	94.0	89.3	91.1	45.9	66.0
3	81.9	73.9	49.3	31.1	45.3	18.5
4	55.6	59.8	78.7	52.9	-7.1	6.1
5	77.6	71.3	72.3	65.9	56.7	59.9
6	75.1	72.8	67.8	73.1	-8.0	13.1
7	41.7	35.9	5.7	50.5	-30.7	-19.3
8	50.3	36.9	46.0	46.5	20.3	16.6
9	-7.9	32.0	58.6	60.4	6.8	0.3
10	49.3	62.1	53.5	60.2	4.7	15.6
11	91.7	92.8	100.0	88.7	22.9	59.9
12	80.9	80.9	86.4	86.7	8.1	-9.8
Mean	59.3	65.2	63.5	63.1	13.3	17.6
SD	29.7	21.0	25.0	18.7	25.9	29.5

Discussion

The study shows that, in asthmatic children, inhaled NS (4 mg) and SCG (10 mg) give a comparable protection from EIA, and that both drugs are more effective than placebo. No further improvement is observed when NS or SCG are administered *via* a large-volume spacer (Fisonair) added to MDI.

Our data are in agreement with other single-dose studies, which showed the effectiveness of NS in preventing EIA both in adults and in children [2–4]. Protection provided by nebulized NS was not dose-dependent, over a range of doses between 0.5–20 $mg \cdot ml^{-1}$, and was similar to that afforded by 4 mg from an MDI [4]. Otherwise, few studies have been designed to compare NS with SCG, which has a well-known protective effect on EIA, and results from such studies are sometimes at variance.

The basis for a theoretical advantage of NS over SCG would be the greater stabilizing effect of NS on mucosal mast cells, which are believed to play a leading role in the pathogenesis of EIA [5, 6]. In EIA, NS is generally found to be of similar effect to SCG [7, 8], although PATEL and ALBAZZAZ [9] reported a significantly higher protection with NS. Our data in children confirm the comparable potency of the two drugs (at the recommended clinical doses) in preventing EIA when administered 30 min before the challenge.

The use of a spacer device in adjunct to MDI has been strongly suggested for children who may fail to benefit from anti-asthmatic therapy because of an incorrect technique of inhalation [12]. Spacer devices have several potential advantages: they dissipate the velocity of an aerosol cloud, allowing sedimentation of larger particles in the chamber, and they also increase drug delivery to peripheral airways, by decreasing the amount lost from impaction in the oropharyngeal cavity. Although Fisonair was designed to improve the delivery of NS and SCG, it did not influence the effects of both the drugs on EIA in the present study. This was probably due to the correct technique by which this selected group of children used MDI, thus allowing optimal drug delivery to airways.

We conclude that NS and SCG have similar effectiveness in EIA in children when administered at the recommended clinical dose, and that no advantage should be expected by the addition of a spacer device to MDI if the technique of inhalation is correct. It would be worth studying whether the same results were obtained

in children who have co-ordination problems with pressurized inhalers.

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