Bronchodilator effect of nebulized sodium cromoglycate in children born prematurely

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Bronchodilator effect of nebulized sodium cromoglycate in children born prematurely. B. Yuksel, A. Greenough. ©ERS Journals Ltd 1993.
ABSTRACT: We wished to determine whether nebulized sodium cromoglycate (SCG) has bronchodilator effects in very young children. In 18 children born prematurely and studied at a median of 15 months of age, thoracic gas volume (TGV) and airways resistance (Raw), were measured and hence specific airways conductance (sGaw) was calculated before (baseline) and after nebulized saline, and then after sodium cromoglycate. sGaw improved significantly in 10 infants after SCG, compared to only in two following saline. These preliminary results suggest that nebulized SCG may have an acute bronchodilator effect in some children born prematurely.
Eur Respir J., 1993, 6, 387–390.

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Sodium cromoglycate (SCG) is an effective prophylactic treatment of asthma in both adults and children [1, 2]. It also seems to be useful in reducing symptoms in children aged less than 2 yrs [3, 4]. In a randomized controlled trial, which involved very young children born preterm, we recently demonstrated that treatment with SCG reduced symptoms and bronchodilator usage, and improved lung function [5]. It has been suggested that SCG may have an acute bronchodilator effect [6], but this is controversial [7]. Recent evidence [8] suggests that preterm infants respond to bronchodilating agents at an earlier age than infants born at term [9]. It is thus possible that the success of SCG in preterm infants [5] may, in part, be due to an acute bronchodilator effect. The aim of this study was to test this hypothesis by monitoring acute changes in lung function in response to nebulized SCG.

Patients

Eighteen very low birthweight children were studied at a median postnatal age of 15 months (range 7–23 months). Their median birthweight was 1,150 g (510–1,490 g) and gestational age 29 weeks (24–33 weeks). At the time of the study, their median weight was 8.6 kg (6.1–12.0 kg) and height 74.2 cm (60–95 cm). In the neonatal period, 15 had developed respiratory distress syndrome (RDS); 12 had been ventilated, with median duration of mechanical ventilation 4 days (0.2–30 days; and median duration of oxygen support for the 15 RDS infants was 20 days (0.1–110 days). Seven developed neonatal chronic lung disease (CLD), *i.e.* they remained

oxygen-dependent at 28 days of age, but none were oxygen-dependent at the time of the study. Seven had had respiratory symptoms: cough and/or wheeze for 3 or 4 days per week for one month; and/or coughed or wheezed for at least two days following all upper respiratory tract infections. No child was receiving bronchodilator treatment or had had symptoms for 24 h prior to the lung function measurements.

The study was approved by the King's College Hospital Ethics Committee.

Material and methods

The children were seen in the Paediatric Respiratory Laboratory. They were sedated with oral chloral hydrate (80–100 mg·kg^{-1}) and lung mechanics were measured during quiet sleep. Measurements were made of thoracic gas volume (TGV) and airways resistance (Raw). Specific airways conductance (sGaw) was then calculated. Measurements were made before (baseline) and 10 min after nebulised normal saline. Thirty minutes later, when lung function had returned to baseline, 20 mg SCG was administered, and lung mechanics were remeasured after a further 20 min. Two ml of either saline or SCG solution was nebulized over 3 min. All solutions were administered *via* an ultrasonic nebulizer (Medic Electronic Nebulizer AC), which has a minimal output of 0.5 ml·min^{-1} and maximal output of 1 ml·min^{-1}; over 60% of the particles delivered are 5 μ or less in size.

TGV and Raw were measured using a whole body plethysmograph (Hammersmith Hospital Infant Whole Body Plethysmograph, Department of Medical Engineering,

Hammersmith Hospital; total volume 90 l). The child breathed through a face mask, connected to a rebreathing bag via a heated pneumotachograph. The heated, humidified rebreathing system was used to avoid box pressure changes due to the heating and cooling of respired gas. The face mask was sealed around the patient's nose and mouth, using silicone putty to ensure an airtight seal. TGV was measured at the end of a normal inspiration and Raw at two-thirds of maximum inspiratory flow, by the techniques of DUBOIS et al. [10] suitably modified for infants. TGV was calculated from five breaths during occlusion; at least five separate occlusions were made. Raw was calculated from at least 10 breaths. Traces were analysed without knowledge of the clinical details. All measurements were corrected for the apparatus dead space including the face mask (15 ml) and resistance (8 $cmH_2O \cdot l^{-1} \cdot s$, measured at flows of between 5–15 $l \cdot min^{-1}$).

Analysis

TGV, Raw and sGaw following normal saline and SCG were compared to the baseline values and differences assessed for statistical significance using the paired Wilcoxon's signed-rank test. The repeatability of TGV, Raw and sGaw were calculated according to the method of BLAND and ALTMAN [11]. From each patient the two baseline measurements of TGV, Raw and sGaw with the greatest difference (i.e. maximum and minimum) for each subject were selected. The difference between the maximum and minimum measurement was calculated for each subject.

The sum of these differences squared was divided by the number of subjects; the square root of the result gave the standard deviation (SD) of the differences. The coefficient of repeatability was calculated as twice the SD. The coefficient of repeatability was 24 ml for TGV, 7.0 $cmH_2O \cdot l^{-1} \cdot s$ for Raw and 0.016 $l \cdot cmH_2O^{-1} \cdot s^{-1}$ for sGaw. The change in Raw or sGaw in response to saline or SCG administration compared to the baseline results was defined as significant for an individual if it was greater than the coefficient of repeatability. The number of infants who had a significant change in Raw/sGaw following saline or SCG were compared and assessed for statistical significance using Fisher's exact test. Comparison was made of the patients who had or had not had a significant improvement in sGaw following SCG and differences assessed for statistical significance using Fisher's exact test or the Wilcoxon rank sum test.

Results

There was no significant difference in the baseline lung function of the symptomatic (median sGaw 0.090, range 0.046–0.225 $l \cdot cmH_2O^{-1} \cdot s^{-1}$) and the asymptomatic (median sGaw 0.106, range 0.069–0.269 $l \cdot cmH_2O^{-1} \cdot s^{-1}$) infants. TGV did not differ significantly from baseline after either normal saline or SCG (p=0.33 and p=0.70, respectively). There was no significant change in Raw or sGaw in the group overall following normal saline, but following SCG mean Raw decreased (p<0.03) and sGaw increased (p<0.04). There was a significant improvement in Raw in two infants and a deterioration in two following

Table 1. — Individual changes of TGV, Raw and sGaw before and after normal saline and after sodium cromoglycate

Pt no.	Pre-saline			Post-saline			Post-SCG		
	TGV ml	Raw $cmH_2O \cdot l^{-1} \cdot s$	sGaw $l \cdot cmH_2O^{-1} \cdot s^{-1}$	TGV ml	Raw $cmH_2O \cdot l^{-1} \cdot s$	sGaw $l \cdot cmH_2O^{-1} \cdot s^{-1}$	TGV ml	Raw $cmH_2O \cdot l^{-1} \cdot s$	sGaw $l \cdot cmH_2O^{-1} \cdot s^{-1}$
1	253	52	0.076	271	52	0.071	286	42[+]	0.083
2	240	40	0.104	230	44	0.099	237	34	0.124*
3	160	54	0.116	160	51	0.123	154	44[+]	0.148*
4	148	25	0.269	133	33*	0.223[+]	121	48*	0.171[+]
5	188	50	0.106	193	49	0.106	194	40[+]	0.129*
6	188	37	0.144	190	33	0.153	220	31	0.147
7	346	31	0.093	350	28	0.102	348	30	0.096
8	372	59	0.046	386	51[+]	0.051	370	40[+]	0.068*
9	250	41	0.098	270	51*	0.073[+]	260	40[+]	0.096*
10	278	33	0.109	244	30	0.137*	244	31	0.132
11	222	20	0.225	230	18	0.242*	236	16	0.265*
12	180	40	0.139	200	34[+]	0.147	160	44*	0.142
13	250	29	0.138	250	31	0.129	282	31	0.114[+]
14	215	58	0.080	218	53	0.087	224	42[+]	0.106*
15	345	34	0.085	340	34	0.087	310	28	0.115*
16	300	37	0.090	310	41	0.077	280	36	0.099*
17	274	43	0.086	310	38	0.085	290	45	0.077
18	400	36	0.069	390	33	0.078	424	22[+]	0.107*
Mean	246	38.4	0.106	249.4	37.7	0.106	246.6	34.5	0.117
Range	148–400	20–59	0.046–0.269	133–390	18–53	0.051–0.242	121–424	16–48	0.068–0.265

*: significant increase; [+]: significant decrease; TGV: thoracic gas volume; Raw: airways resistance; sGaw: specific airways conductance; SCG: sodium cromoglycate.

nebulized saline, but following SCG an improvement in Raw in seven infants (3 symptomatic; 4 asymptomatic) and a deterioration in two (table 1). Two infants had a significant increase in sGaw following nebulized saline, but 10 infants had a significant improvement in sGaw following SCG (p<0.01), (table 1). There were no significant differences in the patients with and without a significant improvement in sGaw following SCG (table 2).

Table 2. – Comparison of patients with and without a significant improvement in sGaw following sodium cromoglycate

	Significant improvement	No significant improvement
Patient n	10	8
Birthweight g	1064	1114
	(510–1490)	(836–1300)
Gestational age	29	29
weeks	(24–33)	(26–31)
Neonatal	1	2
ventilation days	(0–34)	(0–23)
Neonatal oxygen	10	10
dependency days	(0–110)	(0–56)
Postnatal age	16	15
months	(8–20)	(7–23)
Symptomatic n	4	3
Family history	4	3
of asthma n		
Baseline sGaw	0.094	0.124
$l·cmH_2O^{-1}·s^{-1}$	(0.046–0.225)	(0.085–0.269)

Data are mean and range in parenthesis. sGaw: specific airways conductance.

Discussion

These results suggest that SCG may have an acute bronchodilator effect in certain children born prematurely. SCG has previously been noted to have an acute effect on lung function in paediatric patients. In children, SCG produces a significantly raised peak expiratory flow rate [6] and it can cause bronchodilation prior to exercise [12, 13]. SCG has a beneficial effect on airway calibre in recurrently wheezy infants [14], and in infants with bronchopulmonary dysplasia its use attenuates the deterioration in lung mechanics following cold air challenge [15] and improves pulmonary mechanics [16]. The apparent bronchodilating effect of SCG seen in certain patients may be due to a direct action on either cholinergic or irritant receptors [17], or receptors in smooth muscle [6].

Although the effect of SCG on lung mechanics that we have demonstrated is consistent with previous findings in the literature [6, 12–16], it must be appreciated that our study design was not optimal. We recruited a consecutive group of patients from a large prospective follow-up study of all infants with birthweight less than 1,500 g discharged from our neonatal unit. Our group, therefore was heterogenous, and not all subjects were symptomatic or had developed CLD. Interestingly, however, we found

no significant differences between the responders and non-responders to SCG. We had previously demonstrated normal saline to have an acute effect on lung function only 10 min after nebulization [18], but an earlier study had suggested that the effect of SCG may only be identifiable after 20 min [15], and thus our protocol was modified with regard to these timings. We did not randomize the order of administration of the two nebulized solutions, but to minimize bias ensured that lung function had returned to baseline values following administration of nebulized saline before giving the SCG. Only two infants had a significant improvement in sGaw following normal saline, compared to 10 following SCG.

These preliminary results suggest that SCG has an acute bronchodilator effect in certain children born prematurely. Administration of nebulized SCG resulted in a 25% increase in sGaw, this change being similar to the 31% change seen in symptomatic infants following nebulized salbutamol [18], and greater than the 13% change in sGaw following nebulized ipratropium bromide in a similar group of patients. In infants born at term a 21% reduction in sGaw following nebulized water was associated with a deterioration in the patients' clinical condition [19]. Thus, it seems likely that the improvement in sGaw resulting from administration of SCG would be of clinical significance. We have previously found that neither nebulized salbutamol [18] nor ipratropium bromide [20] acutely improve lung function in all children born prematurely; SCG may be useful for such non-responders.

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