Sodium cromoglycate in asthma: correlation between response and serum concentrations

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SUMMARY The clinical response to sodium cromoglycate treatment was compared with its concentration in serum. Twenty five children with asthma entered a 10 week trial of two baseline weeks followed by eight weeks of treatment by the inhalation of 20 mg of sodium cromoglycate spincaps four times a day. Individual clinical response was determined by the differences between baseline and treatment periods of: (a) percentage of symptomless days (Δ score 0); (b) diary derived daily score for four symptoms (Δ DS); and (c) peak expiratory flow rate (Δ PEFR). At the end of the treatment period, patients inhaled a 20 mg spincap of sodium cromoglycate and the technique of inhalation was graded. Concentrations of sodium cromoglycate in serum were measured by radioimmunoassay in samples withdrawn 5 to 120 minutes after inhalation. Δ Score 0, Δ DS, and Δ PEFR correlated significantly with the area under the concentration time curve. Both the area under the sodium cromoglycate concentration time curve and clinical response correlated significantly with inhalation technique score. We suggest that response of children with asthma to inhalation treatment with sodium cromoglycate is correlated to its serum concentrations.

Sodium cromoglycate is an effective drug in the prophylactic treatment of asthma, especially in children. Its efficacy is ascribed to its ability to inhibit degranulation of mast cells in the respiratory tract.^{1–4} It is claimed to be as effective as theophylline,^{5,6} however, a quarter to a third of children appear not to respond to this treatment.^{7,8} This failure could presumably be due to either a true non-responsiveness to the drug or inadequacy in its delivery to target site.

Using radioimmunoassay to measure sodium cromoglycate in normal volunteers it has been shown that concentrations in the blood are very low after oral ingestion.⁹ Inhalation of the drug, however, led to much higher concentrations.^{9,10} We report the results of a prospective study in which the clinical response was compared with concentrations of sodium cromoglycate in serum that were obtained after inhalation of the drug.

Patients and methods

Twenty five children with chronic perennial asthma participated in the study. There were 21 boys and

four girls whose ages ranged from 7 to 14 years, with a mean (SD) of 10.4 (1.9) years. Duration of asthma ranged from one to 12 years, with a mean of 6.3 years. Criteria for inclusion were a history of moderate to severe asthma that was poorly controlled while on routine treatment, needing repeated visits to the emergency room and recurrent hospital admission during the year preceding entry. Patients had a personal or family history of associated atopic disorders and reversibility of airway obstruction as shown by improvement of at least 15% in forced expiratory volume in one second (FEV₁) 15 minutes after inhalation of 2.5 mg salbutamol. None of the children had received sodium cromoglycate previously, nor had they been treated with corticosteroids in the three preceding months.

The study was conducted over a period of 10 weeks. The first two weeks were a baseline period during which the patients were instructed in the inhalation technique of capsules of sodium cromoglycate by a powder inhaler, the spinhaler. The patients were instructed to use the inhaler after a forced expiration, to keep their lips tightly attached to the mouthpiece of the device, to take a deep

forceful inspiration to inhale the powder and to hold their breath for 10 seconds afterwards. Salbutamol inhalation was permitted as necessary. Theophylline was stopped in those using it in order to assess better the effect of sodium cromoglycate as a single prophylactic agent and to exclude improved compliance to theophylline as a cause for the results obtained. Over the next eight weeks, the children inhaled 20 mg sodium cromoglycate spincaps four times a day while continuing to use salbutamol as needed.

The patients recorded the following symptoms in a daily diary on a 0–3 scale of increasing severity: sleep disturbance, cough, wheeze, and impairment of activity. Score 3 was given for each of the following symptoms: severe sleepless night, persistent cough, severe wheezes, and physical disability. Score 0 was given when the patient was asymptomatic. Daily score was determined for each day by the sum of the individual scores given to each symptom (maximum score=12). Twice daily the patients also measured peak expiratory flow rates (PEFR) at home, using a Mini-Wright peak-flow meter. Patients were assessed clinically at entry to the study and at the end of weeks two, six, and 10. During each assessment patients were examined, PEFR was recorded as described above, and FEV₁ was measured by a dry spirometer (Vitalograph). Patients were instructed to withhold the use of bronchodilators for at least 24 hours before their clinic visit. On the fourth visit, the patients inhaled one 20 mg spincap of sodium cromoglycate. The technique of inhalation was assessed on a 0–3 scale taking into consideration strength and length of inspiration, motivation of performance, and positioning of patient's head and inhalation device. Venous blood samples for determination of sodium cromoglycate concentrations were drawn at 0, 5, 10, 30, 60, and 120 minutes after inhalation.

Sodium cromoglycate concentration in the serum was determined by the radioimmunoassay method described by Brown *et al.*¹¹ Plots of the concentrations versus time were constructed, and area under the curve was calculated by the trapezoidal method.¹²

Response to treatment was assessed by three parameters: score 0, daily score (DS), and PEFR. The percentage of symptomless days recorded in the diary was calculated for the baseline period and for the eight treatment weeks, and was termed score 0. Mean daily score was calculated from the patients' diaries for both baseline and treatment periods. Mean PEFR was calculated for baseline and treatment periods. For each patient Δ score 0 and Δ DS were calculated as the differences between individual score 0, and mean daily score during baseline

and treatment periods respectively. Δ PEFR was the difference between individual mean PEFR at treatment and baseline periods, divided by mean PEFR during baseline period and was expressed in per cent.

Results were expressed as mean (SD). Means were compared by Student's *t* test, except for the comparison of means of daily score, where the Mann-Whitney test was used.¹³ A *p* value of less than 0.05 was considered significant.

Informed consent was obtained from the parents. The local hospital ethics committee approved the study.

Results

Table I shows clinical and pharmacokinetic data of the patients. Treatment with sodium cromoglycate produced no side effects. Mean (SD) score 0 in the baseline period was 19.8 (23.3)% and in the treatment period 59.8 (32.3)% similar to the value obtained by Newth *et al.*¹⁴ The rise in mean score 0 during treatment is significant (*p*<0.002). There was no difference in mean score 0 after four or eight weeks of treatment. Mean daily score during the baseline and treatment periods, was 2.64 (1.1) and 0.85 (1.1) respectively (*p*<0.001). Cough and wheeze were the two symptoms which contributed most to the calculated daily score. Mean PEFR during the baseline period was 260 (61) l/minute and during treatment, 307 (76) l/minute (*p*<0.02). FEV₁, which was measured only during the clinic visits, was 69.3 (15.5)% on admission to the trial, 78.6 (19.5)% at the end of the baseline period, and 89.5 (18.2)% at the end of the trial.

Serum sodium cromoglycate concentration determined after inhalation of 20 mg of the drug rose rapidly. In 11 patients it reached a peak five minutes after inhalation, in eight patients 10 minutes after inhalation, and in five patients 15 minutes after inhalation. Peak concentrations varied considerably among the patients (table I). Mean peak sodium cromoglycate concentration was 51 µg/l, and the mean value 120 minutes after inhalation was 13 µg/l. The area under the sodium cromoglycate concentration time curve was calculated for each patient. Individual clinical response measured as the parameters Δ score 0, Δ DS, and Δ PEFR were correlated with the pharmacokinetic parameters: area under the curve, peak sodium cromoglycate concentration, and the clinically convenient parameter of sodium cromoglycate concentration 10 minutes after inhalation (SCG 10 minute).

Table 2 shows that the correlation between Δ score 0 as well as Δ PEFR and all the pharmacokinetic parameters was significant, Δ DS corre-

Table 1 Clinical and pharmacokinetic data of patients

Patient No	Sex/Age (years)	Weight (kg)	Height (cm)	Severity of asthma	Medications*	Δ Score 0† (%)	Δ DS‡	Δ PEFR§ (%)	Technique score	Area under the curve ($\mu\text{g/l}\times\text{hour}$)	Sodium cromoglycate concentration ($\mu\text{g/l}$)	
											Peak	SCG 10 minute
1	M/12	25	128	Moderate	Salbutamol	88	1.4	16	3	79	90	74
2	M/10	29	133	Moderate	Salbutamol, theophylline	36	1.6	16	3	116	68	53
3	M/8	30	134	Moderate-severe	Salbutamol, theophylline	5	-1.0	-19	1	11	13	12
4	M/9	34	137	Severe	Salbutamol, corticosteroids	16	2.2	11	1	22.5	15	15
5	M/10	23	126	Severe	Salbutamol, theophylline, corticosteroids	81	4.2	47	3	101	63	63
6	M/10	25	135	Moderate	Theophylline	60	2.8	9	2	57.5	71	71
7	M/14	38	160	Moderate	Salbutamol, theophylline	6	1.2	50	2	46	66	24
8	M/10	35	140	Moderate-severe	Salbutamol, theophylline	0	1.5	7	0	7.5	10	7
9	F/9	30	135	Moderate-severe	Salbutamol, theophylline, corticosteroids	21	1.3	-7	2	37	52	35
10	M/14	45	160	Moderate-severe	Salbutamol, theophylline, corticosteroids	74	2	19	1	25	18	15
11	M/7	26	126	Moderate	Salbutamol, theophylline	52	0.85	11	2	26.5	21	21
12	M/9	30	134	Moderate-severe	Salbutamol, theophylline	27	0.7	26	2	58.5	50	50
13	F/11	28	127	Moderate	Salbutamol	25	1.5	9	2	46	54	42
14	M/13	46	165	Severe	Salbutamol, theophylline	0	2.75	2	1	32.5	18	13
15	M/9	30	132	Severe	Salbutamol, theophylline, corticosteroids	38	1.75	21	2	60	50	50
16	F/12	42	153	Moderate-severe	Salbutamol, corticosteroids	13	0.3	21	1	36.5	45	45
17	M/12	32	141	Moderate-severe	Salbutamol, theophylline, corticosteroids	33	1.35	6	0	21.5	30	28
18	F/8	36	138	Moderate	Salbutamol, theophylline	44	1.5	7	2	43.5	58	58
19	M/10	40	148	Moderate	Salbutamol	50	2.5	25	3	91.5	105	101
20	M/9	20	137	Severe	Salbutamol, theophylline, corticosteroids	49	4.1	25	2	36.5	61	40
21	M/10	33	145	Moderate-severe	Salbutamol, theophylline	77	2	17	3	85	108	103
22	M/12	40	154	Moderate	Salbutamol	9	0	40	1	40	53	53
23	M/9	23	125	Severe	Salbutamol, theophylline, corticosteroids	74	4	24	3	62.5	59	33
24	M/9	34	137	Severe	Salbutamol, corticosteroids	80	2.7	75	3	68	68	68
25	M/14	33	142	Moderate	Salbutamol	46	1.5	7	3	35	27	27

*Medications taken in the 12 months before sodium cromoglycate.

† Δ Score 0=difference in percentage of symptomless days between baseline and treatment period; ‡ Δ DS=difference in mean diary derived daily score for four symptoms between baseline and treatment period; § Δ PEFR=difference in mean peak expiratory flow rate between treatment and baseline period.

Table 2 Correlations between clinical and pharmacokinetic parameters

	<i>r</i> Value	<i>p</i> Value	No of patients
Δ Score 0* ν area under the curve	0.525	<0.003	24
Δ Score 0 ν peak concentration of sodium cromoglycate	0.527	<0.003	25
Δ Score 0 ν SCG 10 minute	0.561	<0.002	25
Δ DS† ν area under the curve	0.379	<0.035	24
Δ DS ν peak concentration of sodium cromoglycate	0.291	<0.08	25
Δ DS ν SCG 10 minute	0.226	>0.10	25
Δ PEFR‡ ν area under the curve	0.455	<0.015	24
Δ PEFR ν peak concentration of sodium cromoglycate	0.411	<0.02	25
Δ PEFR ν SCG 10 minute	0.361	<0.04	25

* Δ Score 0=difference in percentage of symptomless days between baseline and treatment period; † Δ DS=difference in mean diary derived daily score for four symptoms between baseline and treatment period; ‡ Δ PEFR=difference in mean peak expiratory flow rate between treatment and baseline period.

lated significantly only with the area under the curve. The correlation between Δ score 0 and SCG 10 minute is shown in fig 1 and the correlation between Δ PEFR and area under the curve is shown in fig 2.

In order to determine whether the technique of inhalation of sodium cromoglycate affects clinical response to the drug, the pharmacokinetic parameters and clinical response were correlated with the efficiency of the technique of inhalation. Table 3 shows that highly significant correlations were obtained between the area under the curve, peak concentration of sodium cromoglycate, and SCG 10 minutes, and technique of inhalation. The correlation between the area under the curve and technique of inhalation is shown in fig 3. There is also a correlation between clinical response and inhalation technique, but its significance is smaller (table 3).

Finally, in an attempt to assess the effect of improved delivery of sodium cromoglycate, four patients with low peak sodium cromoglycate concentration were reinstructed in the use of the inhaler. In three patients peak concentrations rose from 19 (10) $\mu\text{g/l}$ to 64 (15) $\mu\text{g/l}$ ($p<0.025$). In one patient it did not change.

Fig 1 Correlation between the difference in percentage of symptomless days during baseline and treatment period (Δ score 0) and concentration of sodium cromoglycate at 10 minutes.

Fig 2 Correlation between the difference in mean peak expiratory flow rate at treatment and baseline periods (Δ PEFR) and sodium cromoglycate area under the concentration time curve.

Table 3 Correlations between pharmacokinetic and clinical parameters and technique of inhalation

	<i>r</i> Value	<i>p</i> Value	No of patients
Area under the curve			
v technique	0.798	<0.0005	24
Peak concentration of sodium cromoglycate			
v technique	0.717	<0.0005	25
SCG 10 minute			
v technique	0.652	<0.0005	25
Δ Score 0*			
v technique	0.671	<0.0005	25
Δ DS†			
v technique	0.410	<0.02	25
Δ PEFR‡			
v technique	0.373	<0.035	25

* Δ Score 0=difference in percentage of symptomless days between baseline and treatment period; † Δ DS=difference in mean diary derived daily score for four symptoms between baseline and treatment period; ‡ Δ PEFR=difference in mean peak expiratory flow rate between treatment and baseline period.

Fig 3 Correlation between sodium cromoglycate area under the concentration time curve and technique of inhalation.

Discussion

Measurement of sodium cromoglycate concentration enables one to determine the relation between drug concentration and response. As the site of action of this drug is not clinically accessible, measurement of sodium cromoglycate in the blood, apparently reflecting its concentration in the bronchioles, may be informative. Indeed, in normal

volunteers it was shown that the concentrations in the blood rise rapidly after inhalation,^{9 10} whereas after oral ingestion blood concentrations are low,⁹ thereby explaining the ineffectiveness of oral sodium cromoglycate in asthma.

Serum sodium cromoglycate concentrations in our young asthmatic patients rose after inhalation of 20 mg sodium cromoglycate and reached a mean peak of 51 μ g/l, compared with a mean

peak of 46 $\mu\text{g/l}$ observed in adult volunteers.⁹ Concentrations declined promptly to a mean of 13 $\mu\text{g/l}$ at 120 minutes after inhalation, in a similar way to that observed in volunteers.⁹⁻¹¹ In contrast, Patel *et al* found that in asthmatic adults four successive inhalations of 5 mg sodium cromoglycate produced peak concentrations of only 5 $\mu\text{g/l}$ which did not decline for 60 minutes after inhalation.¹⁵ The reasons for this discrepancy are not clear.

A correlation was found between individuals' response and pharmacokinetic parameters. The Δ score 0 correlated significantly with all three pharmacokinetic parameters. The correlation between Δ PEFR and these three parameters was also significant, although of lower magnitude. The Δ DS correlated significantly only with the area under the curve which integrates concentration over time.

Spontaneous improvement during baseline period was observed as shown by the FEV_1 values, however, the correlation which was found between the response during the treatment period and the pharmacokinetic parameters, argues for a direct relation between serum sodium cromoglycate concentration and the clinical response observed. Furthermore, this correlation provides evidence for the efficacy of sodium cromoglycate in this group of asthmatic children.

In an attempt to define the basis for the low sodium cromoglycate concentration in some patients, the technique of sodium cromoglycate inhalation was correlated with blood concentrations and with clinical response. Both pharmacokinetic parameters and clinical response correlated significantly with technique of inhalation. Brown *et al* have found that in normal volunteers the sodium cromoglycate area under the curve correlated with peak inspiratory flow rate, however, they state that variation in area under the curve and peak sodium cromoglycate is not solely explained by variation in peak inspiratory flow rate.⁹ Similar data of intra-subject and intersubject variability were recently reported by Neale *et al*.¹⁶ If technique of inhalation in some way or partly reflects peak inspiratory flow rate (which was not measured in our patients), one could argue that low sodium cromoglycate serum concentrations in some patients were the result rather than the cause of the poorer respiratory performance in the poorly responding patients. Peak inspiratory flow rate, however, falls only in severe obstructive airway disease, which did not occur in our patients. In addition, clinical response to sodium cromoglycate in our study was not related to the initial severity of disease. Two of seven patients with severe disease were poor responders (Δ score 0 <20%); this is similar to the proportion

of poor responders in all the patients (seven out of 25, 28%).

It is not inconceivable, however, that severe airway obstruction may impede delivery of sodium cromoglycate to its target site of action. In such circumstances the use of a bronchodilator before inhalation of this drug or the use of special inhalation devices¹⁷ may be considered and studied. No side effects of sodium cromoglycate were observed in this study, neither were dose related side effects observed in worldwide experience over many years.³ Because response seems to be related to sodium cromoglycate concentrations in the blood, administration of larger doses than the recommended ones should also be considered.

This study shows that response to sodium cromoglycate is correlated to its concentration in the blood. Most of the non-responding patients have decreased concentrations of the drug, and in some of them this can be improved by additional training in proper use of the inhaler. There may yet be a few patients who do not respond even to apparently therapeutic concentrations of sodium cromoglycate.

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