Effect of lignocaine, sodium cromoglycate, and ipratropium bromide in exercise-induced asthma

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ABSTRACT Eight patients with exercise-induced asthma participated in a single-blind trial comparing the protective effects of inhaled lignocaine (estimated dose 48 mg), sodium cromoglycate (estimated dose 12 mg), and ipratropium bromide (estimated dose 120 μ g). Saline was used as control. Effects were assessed from the mean maximal percentage fall in forced expiratory volume in one second (FEV₁) and maximal mid-expiratory flow rates (MMFR) after they had run on a treadmill for eight minutes. There was no significant change in baseline FEV₁ or MMFR before each agent was given. Saline, lignocaine, and sodium cromoglycate did not alter the mean baseline FEV₁ or MMFR significantly. Ipratropium caused bronchodilatation with an increase of 16.3% in the mean FEV₁ ($p < 0.001$) and of 43.4% in the mean MMFR ($p < 0.05$). After exercise the maximal percentage falls in FEV₁ (means and SEM) after saline, lignocaine, sodium cromoglycate, and ipratropium bromide were 38.1% (5.0), 34.5% (6.1), 11.3% (3.7), and 19.3% (7.4) respectively. Similarly, the mean maximal falls in MMFR after saline, lignocaine, sodium cromoglycate, and ipratropium bromide were 54.4% (5.2), 52.9% (7.7), 23.6% (6.6), and 32.1% (10.5) respectively. The inhibitory effects of sodium cromoglycate and ipratropium bromide were significant whereas lignocaine failed to produce an effect. These results suggest that mediator release is an important factor in exercise-induced asthma and that in some patients the effects of the mediators may be on the postsynaptic muscarinic receptors. Local anaesthesia of sensory vagal receptors, on the other hand, does not prevent exercise asthma and these receptors do not appear to have any important role in exercise-induced bronchoconstriction.

The exact mechanism of exercise-induced asthma remains unclear; stimulation of a vagal reflex and the release of mast cell mediators in response to exercise have both been postulated.^{1,2} Recent studies have related exercise asthma to hyperventilation and subsequent airway heat loss but have failed to clarify whether the respiratory heat loss stimulates the irritant receptors in the airways or causes mast cell degranulation.³ Local anaesthesia of the upper airways with lignocaine has been shown to inhibit bronchoconstriction induced by inhalation of cold air and by exercise in patients with asthma.^{4,5} Sodium cromoglycate, which suppresses the release of mast cell mediators *in vitro*, is effective in preventing exercise-induced asthma.^{6,7} More recently sodium cromoglycate has been shown to attenuate bronchoconstriction induced by cold air, methacholine, and histamine in asthmatic patients.⁸⁻¹⁰ It has been proposed that this additional effect of sodium cromoglycate may be mediated either directly on the bronchial smooth muscle or through an action on the

cholinergic receptors in the airways. In this study we have compared the effect of inhaled lignocaine, ipratropium bromide, and sodium cromoglycate in eight patients with extrinsic and reproducible exercise-induced asthma.

Patients and methods

Twelve patients with extrinsic and reproducible exercise-induced asthma were included in the trial. Four of these patients had to be excluded because they developed considerable and prolonged bronchoconstriction after inhalation of lignocaine (4 g/l). The remaining eight patients, aged 17-49 years (mean 31.2, SEM 4.0) were studied. Sodium cromoglycate and bronchodilator drugs were discontinued for 24 hours before each test was carried out (patients taking oral or aerosol corticosteroids or antihistamines had been excluded from the study). All the patients were non-smokers and gave informed consent to be studied. Forced expiratory volume in one second (FEV₁) and maximum mid-expiratory flow rates (MMFR) were measured on a water-

sealed spirometer (Godart Pulmotest). The best of three attempts was used for analysis and volumes were corrected to BTPS. Predicted normal values were taken from Cotes¹¹ and Bates *et al.*¹² The exercise test consisted of steady-state running on an inclined treadmill for up to eight minutes. During the exercise the patients breathed through their mouths, their noses being occluded with a clip. The speed of the treadmill was adjusted so that the pulse rate at the end of exercise was 160 beats per minute. The four tests in each patient were completed within seven to ten days to avoid changes in bronchial hyper-reactivity. The temperature on study days was 20–22°C and the relative humidity ranged from 20% to 40%. The study was carried out in a random single-blind fashion with normal saline (9 g/l), lignocaine hydrochloride (40 g/l), sodium cromoglycate nebuliser solution (10 g/l), and ipratropium bromide (0.1 g/l). The drugs were delivered through a Wright nebuliser at a flow rate of 9 l/min (18 lb/in², 124 kPa).

All inhalations were carried out by tidal breathing through the mouth. The estimated doses of lignocaine, sodium cromoglycate, and nebulised ipratropium were 48 mg, 12 mg, and 120 µg respectively. Spirometry was repeated 30 minutes after inhalation and then at 2, 5, 10, 15, and 30 minutes after exercise. Five of the patients were given two minutes' inhalation of 10% of citric acid. Induction of five or more coughs was considered as a positive response. The concentration of citric acid was increased to 20% if there was no cough response. The effects were assessed 30 minutes after lignocaine or saline inhalations. Results of exercise tests were expressed as the maximum fall in FEV₁ and MMFR from the post-drug baseline and analysed with Student's paired *t* test (for both absolute and percentage changes).

Results

Tables 1–3 give the results. There was no significant

Table 1 Effect of saline, lignocaine, sodium cromoglycate, and ipratropium on exercise-induced change in FEV₁ (litres) in eight patients

No	Age	Sex	Predicted FEV ₁	Saline			Lignocaine			Sodium cromoglycate			Ipratropium		
				Baseline A	Baseline B	Postexercise change	Baseline A	Baseline B	Postexercise change	Baseline A	Baseline B	Postexercise change	Baseline A	Baseline B	Postexercise change
1	36	F	2.58	2.56	2.61	-0.70	2.44	2.34	-0.90	2.31	2.18	-0.16	2.44	2.78	-0.07
2	24	M	3.98	4.10	4.08	-1.54	3.85	4.08	-1.87	4.02	4.12	-1.21	3.82	4.27	-1.34
3	32	M	3.82	2.91	2.98	-0.67	2.84	2.74	-0.66	3.08	3.01	-0.13	2.71	3.48	-0.30
4	49	M	3.30	2.71	2.71	-0.66	2.68	2.68	-0.47	2.58	2.60	+0.11	2.11	2.71	-0.34
5	17	M	4.00	3.85	3.45	-2.11	3.28	3.65	-1.84	3.62	3.92	-0.27	3.52	3.62	-1.08
6	44	M	3.83	3.45	3.41	-1.13	3.18	3.05	-0.65	3.18	3.28	-0.67	3.15	3.85	+0.03
7	25	F	3.02	2.51	2.52	-1.32	3.25	2.95	-1.85	2.78	2.71	-0.57	2.51	2.78	-1.91
8	22	F	2.93	3.08	3.01	-1.41	3.25	3.18	-0.50	3.01	3.08	-0.10	3.15	3.75	-0.27
Mean	31.2		3.43	3.15	3.10	-1.19	3.0	3.08	-1.09	3.08	3.11	-0.36	2.93	3.41	-0.66
SEM	4.0		0.19	0.21	0.19	0.18	0.15	0.20	0.23	0.20	0.23	0.15	0.21	0.21	0.24

A — before drug; B — after drug.

Table 2 Effect of saline, lignocaine, sodium cromoglycate, and ipratropium on exercise-induced change in maximal mid-expiratory flow rate (MMFR) (ls⁻¹) in eight patients

No	Predicted MMFR	Saline			Lignocaine			Sodium cromoglycate			Ipratropium		
		Baseline A	Baseline B	Postexercise change	Baseline A	Baseline B	Postexercise change	Baseline A	Baseline B	Postexercise change	Baseline A	Baseline B	Postexercise change
1	3.26	2.55	2.74	-1.37	2.32	2.40	-1.49	2.03	1.75	-0.19	2.36	3.25	-0.13
2	4.40	7.36	6.41	-4.32	6.31	6.44	-4.62	6.31	6.90	-4.07	4.69	8.52	-6.34
3	4.24	2.29	2.32	-0.81	2.08	1.94	-0.69	2.68	2.47	-0.29	1.92	2.90	-0.43
4	3.47	1.56	1.57	-0.51	1.71	1.70	-0.38	1.54	1.77	-0.16	1.20	1.67	-0.34
5	4.61	3.14	2.50	-1.77	2.18	3.06	-2.31	2.79	3.76	-0.97	2.66	2.53	-0.95
6	3.92	1.96	1.91	-0.99	1.63	1.72	-0.65	1.64	1.80	-0.62	1.58	2.35	-0.06
7	3.80	1.90	1.90	-1.26	3.82	2.52	-2.00	2.19	2.17	-0.76	2.16	2.28	-1.80
8	3.50	2.73	2.58	-1.59	3.11	3.24	-1.13	2.83	2.50	-0.08	3.54	5.27	-1.27
Mean	3.90	2.94	2.74	-1.58	2.89	2.88	-1.53	2.75	2.89	-0.89	2.51	3.60	-1.42
SEM	0.17	0.66	0.54	0.42	0.55	0.55	0.51	0.54	0.61	0.47	0.40	0.80	0.76

A — before drug; B — after drug

Table 3 Effect of saline, lignocaine, sodium cromoglycate, and ipratropium on the mean exercise-induced change in FEV₁ and maximal mid-expiratory flow rate (MMFR) in eight patients

Drug	FEV ₁ Mean (± SEM) change (%)	MMFR Mean (± SEM) change (%)
Saline	38.1 (5.1)	54.4 (5.2)
Lignocaine	34.5 (6.1)	52.9 (7.7)
Sodium cromoglycate	11.3 (3.7)	23.6 (6.6)
Ipratropium	19.3 (7.4)	32.1 (10.5)
Saline v lignocaine	NS	NS
Saline v sodium cromoglycate	< 0.01	< 0.01
Saline v ipratropium	< 0.02	< 0.05
Lignocaine v sodium cromoglycate	< 0.01	< 0.01
Lignocaine v ipratropium	< 0.01	< 0.05
Sodium cromoglycate v ipratropium	NS	NS

difference between the mean baseline values of FEV₁ and MMFR before inhalations of saline, lignocaine, sodium cromoglycate, and ipratropium on the four days of exercise testing. Saline, lignocaine, and sodium cromoglycate inhalations did not have a significant effect on the mean FEV₁ or MMFR. Ipratropium caused bronchodilation with an increase in the mean FEV₁ of 16.3% ($p < 0.001$) and mean MMFR of 43.4% ($p < 0.05$).

After exercise the maximal percentage falls in FEV₁ (means and SEM) after saline, lignocaine, sodium cromoglycate, and ipratropium were 38.1% (5.0), 34.5% (6.1), 11.3% (3.7), and 19.3% (7.4) respectively. Sodium cromoglycate ($p < 0.01$) and ipratropium ($p < 0.02$) both significantly inhibited the fall in FEV₁ whereas lignocaine failed to produce an effect. Similarly, the mean maximal percentage falls in MMFR after saline, lignocaine, sodium cromoglycate, and ipratropium were 54.4% (5.2), 52.9% (7.7), 23.6% (6.6) and 32.1% (10.5). The inhibitory effects of sodium cromoglycate and ipratropium bromide were similar and no significant difference was found between the two drugs. When compared with lignocaine, the effects of sodium cromoglycate and ipratropium were significantly different ($p < 0.01$). In five of our eight patients lignocaine suppressed coughing induced by citric acid at 30 minutes, suggesting that the local anaesthesia of the upper airways was effective when the patients were exercised. Sodium cromoglycate and ipratropium were both well tolerated by all subjects.

Discussion

Sodium cromoglycate and ipratropium bromide both significantly inhibited exercise-induced asthma as measured by the fall in FEV₁ and MMFR, whereas local anaesthesia with lignocaine failed to produce an effect. Lignocaine is reported to cause bronchoconstriction in asthmatic patients¹³ and four of the

original 12 patients entering this study had to be excluded because of this. Although no significant improvement was noted in FEV₁ and MMFR after inhalation of lignocaine, all our subjects stated that the sensation of postexercise bronchoconstriction was lessened. The upper airways anaesthesia was effective in our patients as assessed by suppression of coughing induced by citric acid. The dose of lignocaine used in this trial was similar to that used by Enright and his colleagues,⁵ but we were unable to substantiate their observations.

Recent work has suggested that exercise-induced asthma is related to hyperventilation and subsequent airway heat loss, but it remains unclear whether this is due primarily to stimulation of irritant vagal receptors or to a direct effect on mast cell degranulation.^{1 2} While isocapnic hyperventilation does not cause a rise in blood histamine concentrations in asthmatic patients,^{14 15} some workers have shown a rise in histamine after exercise, particularly in patients with asthma.¹⁵⁻¹⁷ The failure of local anaesthesia to modify bronchoconstriction induced by histamine and prostaglandin F_{2α}¹⁸ and also to prevent exercise-induced asthma suggests that the mechanism of post-exercise bronchoconstriction is probably different from that of bronchoconstriction produced by hyperventilation and airway cooling. The beneficial effects of ipratropium bromide and sodium cromoglycate observed in exercise-induced asthma support previous observations.^{1 2 19} The preventive effect of sodium cromoglycate was greater than that of ipratropium bromide, though the difference did not reach significance. The vagal mechanism apparently plays an important part only in patients whose main site of airflow obstruction is in the large airways.^{2 19} In contrast, sodium cromoglycate prevents exercise-induced asthma irrespective of the site of airflow obstruction¹⁹ and also attenuates the bronchoconstriction induced by cold air in asthmatic patients.⁸ Sodium cromoglycate, in addition to

stabilising the mast cell membrane, may suppress the bronchial reactivity to the released mediators and this may explain why it is more effective in preventing exercise-induced asthma than is ipratropium bromide. The failure of local anaesthesia to prevent exercise-induced bronchoconstriction or to modify the effect of inhaled histamine and prostaglandin $F_{2\alpha}$ ¹⁸ suggests that the sensory irritant receptors in the airway do not have a significant role in exercise-induced or chemically induced bronchoconstriction. Blockade of the muscarinic receptor, however, is known to modify both the exercise-induced asthma and non-specific bronchial reactivity. This would imply that in some patients the vagal reflex may be an important component of bronchoconstriction and that this effect is possibly mediated through the postsynaptic muscarinic receptors.

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