Calcium antagonists in exercise-induced asthma

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Abstract

Ten patients with exercise-induced asthma participated in a single-blind trial comparing the protective effects of inhaled verapamil (estimated dose 3 mg) and sodium cromoglycate (estimated dose 12 mg). Saline was used as control. Effects were assessed from the mean maximal percentage fall in forced expiratory volume in one second (FEV_1) after running on a treadmill for eight minutes.

There was no significant change in baseline FEV_1 values after each agent. In the exercise periods, however, FEV_1 fell by 45·4% (SEM 4·0) after saline inhalation, 18·4% (5·1) after sodium cromoglycate, and 16·7% (4·3) after verapamil. The inhibitory effects of sodium cromoglycate and verapamil were comparable and significantly different from saline ($p < 0.02$ and $p < 0.01$ respectively). Nevertheless, considerable intrasubject variability was observed.

The findings suggest that mediator release, which is calcium dependent, may play an important part in exercise-induced asthma, and calcium antagonists may inhibit post-exercise bronchoconstriction by their blocking effect on calcium channels.

Introduction

Recent work has related exercise-induced asthma to hyperventilation[1] and subsequent airway heat loss,[2] but whether this is primarily due to stimulation of irritant vagal receptors or to a direct effect on mast-cell degranulation remains to be determined. Sodium cromoglycate, which prevents mediator release from the mast cell,[3] is more effective than anticholinergic drugs in preventing exercise-induced asthma.[4] This observation supports the view that mediator release may be an important mechanism in post-exercise bronchoconstriction.[5]

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The reaction sequence in the activation of mast cells and the liberation of chemical mediators such as histamine, slow-reacting substance of anaphylaxis, and prostaglandins links calcium ion influx from extracellular medium.[6] The secretion of histamine can also be initiated by movement of calcium ions from the extracellular to intracellular compartment of mast cells even in the absence of antigen.[7] Foreman and Garland[8] postulated that sodium cromoglycate may also act on the calcium-entry pathway. Calcium antagonists such as verapamil and nifedipine selectively inhibit calcium ion influx across the cell membrane and suppress calcium-dependent smooth-muscle excitation.[9] I have compared the effects of inhaled verapamil and sodium cromoglycate on post-exercise bronchoconstriction in 10 patients with extrinsic bronchial asthma.

Patients and methods

Ten patients aged 14 to 52 years (mean 26·3; SEM 3·4) with bronchial asthma and reversible airflow obstruction were studied. All were non-smokers and gave informed consent. Patients taking oral or aerosol corticosteroids were excluded. Each patient gave a positive reaction to skin-prick tests with inhalant allergens and had a blood eosinophil count of over $0{\cdot}5 \times 10^9$/l (500/mm³). Sodium cromoglycate and bronchodilator drugs were discontinued for 24 hours before each test. Forced expiratory volume in one second (FEV_1) was measured with a water-sealed spirometer (Godart Pulmotest). The best of three attempts was used for analysis and volumes were corrected to body temperature and pressure, saturated. Predicted normal values were taken from Cotes.[10]

Exercise testing consisted in steady-state running on an inclined treadmill (10°) for up to eight minutes. Speed was adjusted so that pulse rate at the end of exercise was at least 170-180/min (submaximal work load). The same setting and duration were used for each test in any one patient. The three tests in each patient were completed within a week. Room temperature on study days varied between 20 and 22°C, but humidity was not recorded. The study was carried out in random, single-blind fashion using saline (9 g/l), sodium cromoglycate nebuliser solution (10 g/l), and verapamil (2·5 g/l). The drugs were delivered through a Wright nebuliser driven by compressed air at 8 l/min. All inhalations were carried out for five minutes at tidal breathing. The estimated doses of sodium cromoglycate and verapamil nebulised were 12 mg and 3 mg respectively. Spirometry was repeated 30 minutes after inhalation, and then 2, 5, 10, 15, and 30 minutes after exercise. Results of exercise tests were expressed

TABLE I—*Effect of saline, sodium cromoglycate, and verapamil on exercise-induced fall in FEV_1 in 10 patients. (Baseline data before and after inhalation expressed as absolute values (l) with percentage of predicted in parentheses)*

Case No, sex, and age			Saline			Sodium cromoglycate			Verapamil		
			Baseline		Change	Baseline		Change	Baseline		Change
			Before	After		Before	After		Before	After	
1	F	32	2·18 (83·8)	2·18 (83·8)	−1·01	1·87 (71·9)	1·97 (75·8)	−0·70	2·08 (80·0)	2·14 (82·3)	−0·22
2	F	24	2·78 (89·7)	2·61 (84·2)	−0·79	2·52 (81·3)	2·40 (77·4)	−0·43	2·51 (81·0)	2·68 (86·5)	−0·24
3	F	32	2·21 (85·0)	2·25 (86·5)	−1·18	2·54 (97·7)	2·54 (97·7)	−0·20	2·48 (95·4)	2·43 (93·4)	−0·15
4	M	24	4·32 (99·3)	4·30 (98·8)	−2·11	4·52 (103·9)	4·72 (108·5)	−1·56	3·35 (77·0)	3·28 (75·4)	−0·67
5	M	26	2·04 (51·6)	2·10 (53·2)	−0·56	2·85 (72·2)	2·97 (75·2)	−1·12	2·51 (63·5)	2·24 (56·7)	−0·79
6	F	22	2·58 (83·2)	2·60 (83·9)	−1·10	2·14 (69·0)	2·16 (69·7)	−0·08	3·05 (98·4)	3·25 (104·8)	−0·47
7	F	15	3·08 (86·8)	3·05 (85·9)	−0·97	2·88 (81·1)	3·35 (94·4)	−0·10	3·28 (92·4)	2·88 (81·1)	−0·20
8	M	52	1·60 (57·0)	1·65 (58·7)	−0·87	1·27 (47·5)	1·33 (53·6)	−0·38	1·22 (43·6)	1·39 (49·6)	−0·28
9	F	14	3·25 (104·2)	3·05 (95·5)	−1·96	3·11 (102·9)	3·03 (117·9)	−0·74	2·71 (86·9)	2·61 (83·6)	−1·14
10	F	22	3·48 (124·3)	3·38 (120·7)	−1·97	3·21 (111·1)	3·68 (108·2)	+0·30	3·48 (129·6)	3·38 (127·8)	−0·34
Mean		26·3	2·75 (86·5)	2·71 (85·0)	−1·25	2·69 (83·9)	2·81 (87·8)	−0·50	2·67 (84·8)	2·63 (84·1)	−0·45
SEM		3·4	0·25 (6·7)	85·0 (6·1)	0·18	0·27 (6·3)	0·30 (6·5)	0·17	0·21 (7·2)	0·19 (7·0)	0·10

SEM = One standard error of mean.

as the maximum fall in FEV_1 from the post-drug baseline and analysed with Student's paired t test.

Results

Tables I and II give the results. There was no significant difference between the mean baseline values of FEV_1 before and after inhalation of saline, sodium cromoglycate, and verapamil on the three days of exercise testing.

TABLE II—*Effect of saline, sodium cromoglycate, and verapamil on mean exercise-induced fall in FEV_1 in 10 patients. (Baseline data before and after inhalation expressed as absolute values (l) with percentage of predicted in parentheses)*

	Mean baseline FEV_1		SEM		Mean change (%)
	Before	After	Before	After	
Saline	2·75 (86·5)	2·71 (85·0)	0·25 (6·7)	0·24 (6·1)	45·4 (4·0)
Sodium cromoglycate	2·69 (83·9)	2·81 (87·8)	0·27 (6·3)	0·30 (6·5)	18·4 (5·1)*
Verapamil	2·67 (84·8)	2·63 (84·1)	0·21 (7·2)	0·19 (7·0)	16·7 (4·3)†

SEM = One standard error of mean.
*Compared with saline: $p < 0·02$.
†Compared with saline: $p < 0·01$.

After exercise the mean maximal percentage falls in FEV_1 (SEM) after saline, sodium cromoglycate, and verapamil were 45·4 (4·0), 18·4 (5·1), and 16·7 (4·3) respectively. Sodium cromoglycate ($p < 0·02$) and verapamil ($p < 0·01$) significantly inhibited the mean percentage fall in FEV_1. The inhibitory effect of sodium cromoglycate and verapamil was comparable, and no significant difference was found between the two drugs. In case 5, however (table I), both sodium cromoglycate and verapamil failed to have an effect on exercise-induced fall in FEV_1. There was considerable intrasubject variability in the response to verapamil and sodium cromoglycate, verapamil offering better protection in five patients (cases 1, 2, 3, 4, and 8) and sodium cromoglycate proving superior in the remaining four (cases 6, 7, 9, and 10). Both agents were tolerated well by all subjects, apart from a slight bitter taste with verapamil.

Discussion

Verapamil and sodium cromoglycate significantly inhibited exercise-induced asthma as measured by fall in FEV_1 in nine patients. Both drugs, however, failed in case 5. There was considerable variability in response to the two agents among the patients studied, verapamil offering better protection in five and sodium cromoglycate proving superior in the remaining four.

The mechanism of exercise-induced asthma is unknown; both a vagal reflex through stimulation of irritant receptors and mediator release from the lung mast cells have been suggested. The vagal mechanism is apparently significant only in patients whose main site of airflow obstruction is in the large airways.[4 11] In contrast, sodium cromoglycate prevents exercise-induced asthma in most patients.[4] The close correlation between bronchial hyperreactivity to exogenous histamine and exercise[12] and the protective effect of sodium cromoglycate suggests that mediator release has an important role in exercise-induced asthma. This is further supported by reduced bronchoconstrictor response when the exercise is repeated at short intervals, suggesting depletion of mediator stores.[13]

The activation of the mast cell on bridging of the membrane-bound IgE antibody to antigen results in calcium ion influx. Furthermore, stimulation of serine esterase and release of chemical mediator require free calcium ions within the mast cell.[7] The absence of calcium ions inhibits mediator release from mast cells in vitro. Similarly, flavones which interfere with calcium ion influx through inhibition of calcium-dependent adenosine triphosphatase also inhibit histamine release from mast cells when challenged with an appropriate antigen.[14] On the other hand, cholinergic stimulation with acetylcholine enhances mediator release, which is associated with an increase in 3′,5′-cyclic guanosine monophosphate.[15] In some tissues an increase in intracellular calcium ions is associated with a rise in 3′,5′-cyclic guanosine monophosphate.[16] The common effective stimulus to the mast cell may therefore be the entry of calcium ions.

Verapamil inhibits transmembrane influx of calcium ions, and in various smooth-muscle preparations it produces relaxation and suppression of calcium-dependent membrane excitation.[9] My observations suggest that verapamil, by blocking transmembrane calcium ion influx, may prevent both the mediator release from the mast cell in response to exercise and the effects of these mediators on the bronchial smooth muscle. Similarly, the beneficial effect of sodium cromoglycate in exercise asthma may also be mediated through its action on the calcium ion channels, as suggested by Foreman and Garland.[8] Studies on calcium antagonists in experimental asthma should further elucidate the role of calcium and its relation to beta-adrenergic and cholinergic mechanisms in asthma.

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