Effect of inhaled saline, sodium cromoglycate, salbutamol, isoxsuprine, and isosorbide dinitrate on exercise induced fall in forced expiratory volume in one second (FEV₁) in seven patients. (Data before and after expressed as absolute values (l) and postexercise change as percentage)

	Baseline FEV ₁ in l (SEM)		Maximal percentage fall in FEV ₁ * (SEM)		p
	Before	After			
(n = 6)					
Saline	2.99 (0.40)	2.95 (0.39)	31 (4.7)	Saline v isoxsuprine	0.01
Salbutamol	3.01 (0.51)	3.69 (0.45)	3 (2.2)	Saline v sodium cromoglycate	0.01
Sodium cromoglycate	3.15 (0.49)	3.26 (0.51)	8 (4.7)	Saline v salbutamol	0.001
Isoxsuprine	3.29 (0.33)	3.41 (0.43)	15 (9.4)	Isoxsuprine v sodium cromoglycate	0.2 (NS)
				Isoxsuprine v salbutamol	0.05
				Salbutamol v sodium cromoglycate	0.01
(n = 7)					
Saline	3.13 (0.34)	3.08 (0.45)	36.9 (4.9)	Saline v isosorbide	0.05
Salbutamol	3.11 (0.46)	3.65 (0.50)	4.3 (1.3)	Saline v sodium cromoglycate	0.05
Sodium cromoglycate	3.29 (0.54)	3.29 (0.58)	15.1 (8.13)	Saline v salbutamol	0.001
Isosorbide	3.44 (0.54)	3.19 (0.49)	20.5 (5.16)	Salbutamol v sodium cromoglycate	0.005
				Salbutamol v isosorbide	0.01
				Isosorbide v sodium cromoglycate	0.2 (NS)

*Maximal changes in FEV₁ calculated from postdrug baseline.

Patients, methods, and results

We studied seven patients aged 14-49 years with extrinsic and reproducible exercise induced asthma. Patients taking oral or aerosol corticosteroids, anti-histamines, and anticholinergic drugs were excluded. Sodium cromoglycate and bronchodilator drugs were discontinued for 24 hours before each test. Forced expiratory volume in one second (FEV₁) was recorded on a water sealed spirometer (Godart Pulmotest). Exercise test consisted in steady state running on a treadmill at submaximal work loads for up to eight minutes under controlled conditions of temperature and humidity. The study was carried out in a random single blind fashion using saline (9 g/l), sodium cromoglycate nebuliser solution (10 g/l), salbutamol nebuliser solution (5 g/l), isosorbide dinitrate (10 g/l), and isoxsuprine (5 g/l). The drugs were delivered through a Wright nebuliser driven by compressed air at 10 l/min at tidal breathing for five minutes. The estimated doses of sodium cromoglycate, salbutamol, isosorbide dinitrate, and isoxsuprine nebulised were 12 mg, 6 mg, 12 mg, and 6 mg, respectively. Spirometry was repeated at 30 minutes after inhalation, then at 2, 5, 10, 15, and 30 minutes after exercise. The results of the tests were expressed as maximal percentage fall in FEV₁ from the postdrug baseline and analysed with Student's paired *t* test.

The effects of saline, salbutamol, sodium cromoglycate, and isoxsuprine were studied in six patients and the effects of saline, salbutamol, sodium cromoglycate, and isosorbide dinitrate in seven (table). The mean baseline FEV₁ before drug inhalation was comparable on all days of exercise testing and no significant difference was noted. Saline, sodium cromoglycate, isoxsuprine, and isosorbide dinitrate also did not affect the mean baseline FEV₁ significantly. As expected, salbutamol had a significant bronchodilator effect (*p* < 0.001). In six patients the maximal mean percentage falls in FEV₁ (SEM) after saline, salbutamol, sodium cromoglycate, and isoxsuprine were 31 (4.7)%, 3 (2.2)%, 8 (4.7)%, and 15 (9.4)%, respectively. The preventive effect of sodium cromoglycate and isoxsuprine was significant and no difference was noted between the two treatments. Salbutamol afforded the greatest protection of all treatments. The difference between salbutamol and sodium cromoglycate and between salbutamol and isoxsuprine was also significant.

In seven patients the maximal mean percentage falls in FEV₁ (SEM) after saline, salbutamol, sodium cromoglycate, and isosorbide dinitrate were 36.9 (4.9)%, 4.3 (1.3)%, 15.1 (8.1)%, and 20.5 (5.2)%, respectively. The preventive effect of sodium cromoglycate and isosorbide dinitrate was significant and no difference was noted between the two treatments. Salbutamol again offered the greatest protection of all treatments. The difference between salbutamol and sodium cromoglycate and between salbutamol and isosorbide dinitrate was also significant.

Comment

Isosorbide dinitrate and isoxsuprine given by inhalation afforded significant protection against exercise induced asthma in the patients studied, the beneficial effect being statistically comparable to that given by sodium cromoglycate. Salbutamol was, however, more effective in inhibiting exercise induced bronchoconstriction compared with sodium cromoglycate, isoxsuprine, and isosorbide dinitrate.

Isosorbide dinitrate and isoxsuprine are potent vasodilators³⁻⁵; isosorbide dinitrate acts directly on the bronchial smooth muscle, causing relaxation, whereas isoxsuprine is primarily an alpha blocking agent but with some weak inherent beta agonistic activity. Any action they are likely to have on mast cell membranes is probably minimal and the failure to observe bronchodilation after inhaling these drugs implies that at the dose used they do not relax human bronchial smooth muscle. Our observations imply that the protection afforded in exercise induced asthma is a result of inhibition of the bronchoconstrictor response produced by airways cooling or mediator release or both.

In conclusion, therefore, drugs which act purely on the bronchial

smooth muscle may modify exercise induced asthma, showing that it is important to be sure of the exact site of action of pharmacological agents before making assumptions about the mechanisms of exercise asthma from pharmacological experiments. Finally, our study suggests that isosorbide dinitrate would be a safe and indeed an effective preparation in patients with both chronic obstructive airways disease and ischaemic heart disease.

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Dysphagia: a further symptom of hypercalcaemia?

Carcinoma of the bronchus can produce dysphagia by direct compression of the oesophagus or by pressure from enlarged mediastinal lymph nodes. We report on two cases of bronchial carcinoma in which dysphagia was the predominant symptom and investigation failed to show any obstruction. Both patients, however, were found to have appreciable hypercalcaemia, and correction of this resulted in a rapid return of normal swallowing.

Case reports

Case 1—A 61 year old man developed pain in his right lateral ribs and total dysphagia for solids 10 months after a right upper lobectomy for a squamous carcinoma of the bronchus. A chest x ray film showed an opacity in the right upper zone with destruction of the right fifth and sixth ribs, but barium swallow showed a normal oesophagus with normal peristaltic waves and no evidence of obstruction. Biochemical profile was normal apart from a raised serum calcium concentration of 3.5 mmol/l (14 mg/100 ml) (normal 2.1-2.65 mmol/l (8-11 mg/100 ml)) and raised alkaline phosphatase activity of 163 IU/l (normal 28-128 IU/l). He was treated with high dose corticosteroids and intravenous fluids; his swallowing improved dramatically and had returned to normal within three days. He was given a short course of radiotherapy to the recurrent tumour but subsequently developed wide-

spread metastases and died two months later, having remained normocalcaemic and swallowed normally until death.

Case 2—A 50 year old man developed lymphadenopathy in the left supraclavicular fossa due to squamous carcinoma secondary to a symptomless primary tumour of the left main bronchus. The nodes were treated with palliative radiotherapy, but two months later he developed total dysphagia for solids, anorexia, and nausea. Examination showed some residual lymphadenopathy but was otherwise unremarkable; a chest x ray film, however, showed a primary carcinoma in the left hilar region and multiple bone metastases. Barium swallow showed free flow of barium with no mechanical hold up but some slight muscular incoordination in the pharynx. A biochemical profile showed calcium concentration 3.8 mmol/l (15 ng/100 ml), alkaline phosphatase activity 200 IU/l, urea concentration 17.9 mmol/l (108 mg/100 ml) (normal 2.0-8.1 mmol/l (12-49 mg/100 ml)), and glutamic oxaloacetic transaminase activity 315 IU/l (normal 5-45 IU/l). Treatment with intravenous fluids, high dose steroids, and mithramycin corrected the hypercalcaemia, and his dysphagia had gone completely after five days and he was discharged home. He had no further problems with dysphagia, but died a month later from generalised disease. Postmortem examination confirmed a squamous cell carcinoma of the left main bronchus with widespread metastases but with a normal oesophagus that was not obstructed.

Comment

These two cases were remarkable in the severity of the dysphagia and its rapid improvement after the serum calcium concentration was corrected. Constipation is common in patients with hypercalcaemia and may be related to dehydration and anorexia. The amount of acetylcholine released from nerve endings depends directly on the calcium concentration, and there may be a neuromuscular effect as well. In our cases there was no mechanical obstruction in the oesophagus, and the prompt relief of symptoms on correction of the hypercalcaemia leads us to suggest that the dysphagia was related to an effect of the hypercalcaemia, possibly in the neuromuscular junction, and that dysphagia might be considered as yet another symptom of hypercalcaemia.

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Dietary lactose and the child with abdominal pain

Recurrent abdominal pain affects 10-15% of children and is a frequent complaint to both the general practitioner and paediatrician. Lactose intolerance has been suggested as an important factor in its aetiology,¹ and our study investigates this hypothesis.

Patients, methods, and results

We studied all children over the age of 3 who for the previous three months had had recurrent periumbilical pain occurring more than once every four days. Over two years 39 children were seen. In group 1 (21 children) several investigations were performed, including an oral lactose tolerance test using a dose of 2 g lactose/kg body weight to a maximum of 50 g. A normal response is a rise in the blood glucose concentration at 60 minutes of more than 1 mmol/l (18 mg/100 ml) over the fasting value. During the test the children were asked to record abdominal pain, diarrhoea, or an increase in flatus. Simultaneously a breath hydrogen analysis was performed using a single breath method,² in which a rise of more than 20 parts per million (ppm) at 90 minutes was considered abnormal.

Over the next three months the child and his parents were asked to keep a daily score card of episodes of abdominal pain, diarrhoea, or increased flatus. The child's intake of products containing lactose was recorded on the same card. The cards were collected and a fresh one issued at two week intervals by the same physician. For the first two weeks the child continued with his normal diet. During the third and fourth weeks the child took a lactose free diet. While taking this diet, during the fifth and sixth weeks the child received a tonic. The tonic contained either lactose in a dose of 2 g/kg or a similarly flavoured placebo. The lactose and placebo were allocated at random using a double blind, single crossover design. After three months the parents were asked if their child's symptoms were better, worse, or the same. The 18

children in group 2 were seen only once in the hospital clinic. After a full history had been taken and examination performed the family was reassured and then discharged from the clinic. Three months after presentation the parents were contacted and asked about the child's symptoms in a similar manner to the children in group 1. The two groups were comparable in age (mean 10.6 ± SD 2.6 and 10.2 ± 2.9 years, respectively), sex ratios, and race.

Eight children had an abnormal lactose tolerance test result, four of them complaining of pain, but only one said that the pain mimicked her original complaint. Only these four children, however, had an abnormal breath hydrogen estimation (table). The other four children who had an abnormal lactose tolerance test result but no pain had normal breath hydrogen estimations.

Outcome of investigations in children with abdominal pain in relation to lactose tolerance test results

	Group 1		Group 2
	Abnormal lactose tolerance	Normal lactose tolerance	
No of children	8	13	18
Abdominal pain after lactose tolerance test	4	0	
Abdominal pain mimicking symptoms	1	0	
Breath hydrogen > 20 ppm at 90 min	4	0	
Decreased pain with lactose free diet	1	4	
Increased pain with lactose tonic	1	2	
Improved after three months	2	7	8

One third of the children claimed benefit from the lactose free diet, but this was not correlated with results of the lactose tolerance test, breath hydrogen estimation, or response to lactose challenges. There was no difference in the number of children claiming relief from the placebo or lactose containing tonic. Three months after presentation nine of the 21 children in group 1 had improved, according to their parents. Similarly eight children in group 2 reported an improvement. None of the parents reported that their child's symptoms had increased in severity.

Comment

Although similar to studies in the United States,³ ours indicated that lactose malabsorption is an infrequent cause of recurrent abdominal pain, and it is easy to identify the few children in whom it is causing troublesome symptoms. These children, however, do not need complicated hospital investigations to establish their intolerance. Their lactose tolerance test results and breath hydrogen estimations were less reliable in identifying such children than the simple administration of a lactose challenge, which could have been done by the general practitioner or as an outpatient. We agree with the view expressed recently⁴ that the approach of the child presenting with recurrent abdominal pain should be primarily psychosomatic. Our group of children investigated in hospital did no better than those children who were managed conservatively and in whom expenditure of Health Service resources was considerably less.

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