

# Sodium cromoglycate in nocturnal asthma

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**ABSTRACT** To investigate whether mast cell degranulation was important in producing nocturnal asthma, the effect of a single high dose of nebulised sodium cromoglycate on overnight bronchoconstriction, oxygen saturation, and breathing patterns in eight patients with nocturnal wheeze was examined. The study took the form of a double blind placebo controlled crossover comparison. Treatment with cromoglycate did not reduce the overnight fall in FEV<sub>1</sub> or FVC, although it was associated with improved nocturnal oxygenation. This study suggests that mast cell degranulation may not be important in the pathogenesis of nocturnal asthma.

Patients with nocturnal asthma have been reported to have raised concentrations of plasma histamine at night.<sup>1</sup> This has been interpreted as indicating that mast cell degranulation is important in the production of overnight bronchoconstriction. If this is true then the mast cell stabilising agent sodium cromoglycate<sup>2</sup> may specifically prevent nocturnal asthma. We have therefore studied the effect of a high dose of nebulised cromoglycate on overnight bronchoconstriction, oxygen saturation, and breathing patterns in patients with nocturnal asthma.

## Methods

We studied eight patients (aged 18-62 years) with a history of regular nocturnal awakenings with wheeze and breathlessness (table). All had had symptoms of asthma in childhood. All had positive skin test responses to at least two common allergens; none was taking sodium cromoglycate, and none inhaled bronchodilators for at least six hours before each study. None had had an exacerbation of asthma for at least six weeks before the study and in all the FEV<sub>1</sub> before sleep was within 15% of the value recorded at previous outpatient visits when they were in a stable clinical state.

The patients reported to the sleep laboratory on two pairs of two consecutive nights, seven to 14 days apart, the first of each pair of nights being for acclimatisation; data from the second of each pair only are reported. In a double blind randomised crossover

study each patient received 160 mg (8 ml) of 2% sodium cromoglycate or 8 ml of n saline via a facemask from a Wright nebuliser, nebulised to dryness, one hour before the light was turned out. Nebulisation took 20-30 minutes to complete.

A vitalograph spirometer was used to measure FEV<sub>1</sub> and FVC, and the best of three results was used. Sleep duration and quality was assessed by conventional criteria.<sup>3</sup> Oxygen saturation was recorded using a Hewlett Packard 47201A ear oximeter<sup>4</sup> and breathing patterns were recorded and analysed as previously described.<sup>5</sup> Values are given as means with standard deviations in parentheses. Comparisons between measurements on the treatment and placebo nights were made using Wilcoxon's rank sum test.

## Results

**Overnight change in FEV<sub>1</sub> and FVC** In every patient FEV<sub>1</sub> fell overnight after treatment with placebo (mean 2.5 (1.6)l before sleep falling to 1.8 (1.7)l on awakening;  $p < 0.05$ ) but FEV<sub>1</sub> also fell in all patients except one, in whom there was no change, with sodium cromoglycate (mean 2.4 (1.5) falling to 1.9 (1.2)l;  $p < 0.05$ : fig 1). Similar changes occurred in FVC (3.8 (2.1) to 3.0 (1.8)l with placebo; 3.9 (2.0) to 3.2 (1.8)l with cromoglycate;  $p < 0.05$  for both). There was no significant difference in morning FEV<sub>1</sub> or FVC values or in the overnight changes in FEV<sub>1</sub> or FVC between sodium cromoglycate and placebo.

**EEG sleep stages** The study time was similar on the two nights (placebo 373 (31), cromoglycate 379 (25) min). Sodium cromoglycate did not affect sleep duration or quality.

**Arterial oxygen saturation** Although there was no significant difference in the oxygen saturation when

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Accepted 27 September 1985

## Physical characteristics of patients studied (with symbol for each used in figures)

Patient No	Age (y)	Sex	Height (m)	FEV <sub>1</sub> (l)	FVC (l)	Treatment
1 ■	62	M	1.83	1.1	2.5	B, S, I, PN
2 △	22	M	1.8	3.5	5.6	B
3 ●	28	M	1.68	3.9	5.1	B
4 □	28	M	1.9	5.5	7.8	B
5 ○	18	M	1.62	1.1	2.6	S, B
6 ▽	24	F	1.7	1.6	2.1	B, I, S
7 ▼	60	F	1.69	1.8	2.5	B, S
8 ▲	60	F	1.49	1.4	2.1	B, S

B—inhaled  $\beta_2$  agonist; I—inhaled ipratropium; S—inhaled corticosteroids; PN—oral prednisolone < 10 mg/day.

patients were awake (placebo 95 (2), cromoglycate 95% (3%)), the fall in oxygen saturation from the mean level when they were awake to the lowest saturation during sleep was significantly less during the cromoglycate night than during the placebo night (maximal fall in oxygen saturation 6% (3%) after cromoglycate, 8% (5%) after placebo;  $p < 0.05$ ; fig 2). Five of the eight subjects had fewer hypoxaemic episodes on the cromoglycate night but the number of episodes was unchanged in the other three ( $p > 0.05$ ).

**Irregular breathing** Sodium cromoglycate did not al-

ter the duration of irregular breathing or the number of apnoeic episodes.

### Discussion

This study shows that sodium cromoglycate, used in

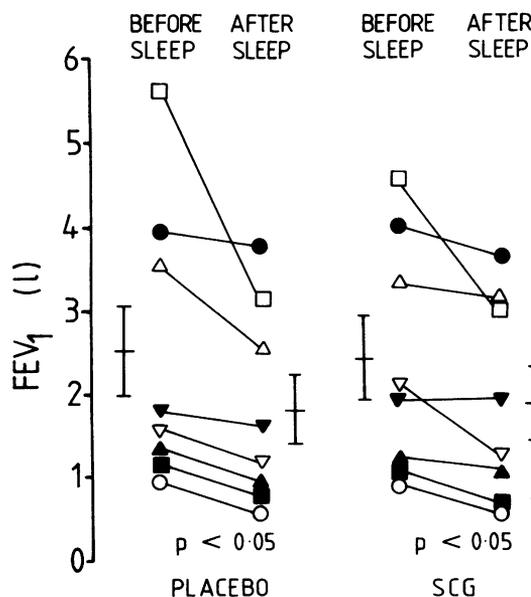


Fig 1 FEV<sub>1</sub> before and after sleep in the eight asthmatic patients on the placebo night and after inhaling 160 mg of sodium cromoglycate (SCG): results from individual patients (identified in the table by the same symbols).

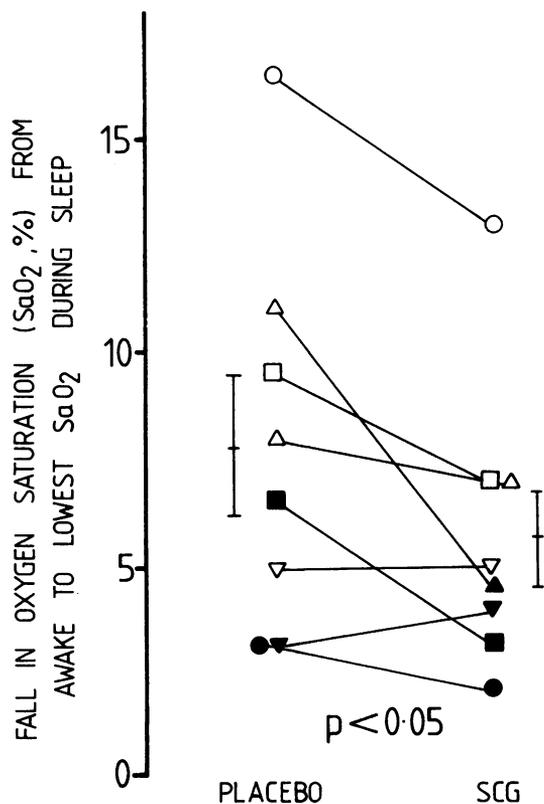


Fig 2 Overnight fall in oxygen saturation on the placebo night and after inhalation of 160 mg of sodium cromoglycate (SCG) showing that desaturation was less on the SCG night: results from individual patients (identified in the table by the same symbols).

high dosage, did not influence overnight bronchoconstriction in patients with chronic stable asthma. The dose of cromoglycate was chosen because it exceeds the dose that affords maximal protection against exercise induced asthma.<sup>6</sup> As one of the actions of sodium cromoglycate is to stabilise mast cells,<sup>2,7</sup> we suggest that this result casts doubt on the notion that nocturnal asthma is caused by release of mediators from mast cells permitted by the circadian drop in circulating adrenaline.<sup>1</sup> The mechanisms of nocturnal asthma remain unclear.<sup>8</sup>

This study confirmed the observation that asthmatic patients become mildly hypoxaemic during sleep<sup>5</sup> and showed that treatment with sodium cromoglycate was followed by improved nocturnal oxygenation. The means by which it improved oxygenation without changing FEV<sub>1</sub> is unclear. There was no evidence that cromoglycate altered breathing patterns, although minor changes in ventilation between the two nights would not be detected by this technique. An alternative explanation is that cromoglycate might have dilated small airways, thus improving ventilation-perfusion matching while having no effect on large airway calibre, the principal determinant of FEV<sub>1</sub>.

This study shows that sodium cromoglycate is ineffective in the treatment of nocturnal asthma when given in a single high dose. The results do not support the theory that mast cell degranulation is central to the pathogenesis of nocturnal asthma.

We gratefully acknowledge the financial support of Fisons PLC Pharmaceutical Division.

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