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Short reports

Is sodium cromoglycate effective in nocturnal asthma?

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Nocturnal asthma is potentially dangerous[1 2] and may be difficult to treat. Slow release oral preparations of methylxanthines[3] or high dose aerosol treatment with β_2 stimulants[4] have been advocated. In our experience, however, both of these groups of drugs may be quite ineffective in some patients and many patients cannot tolerate methylxanthines in effective doses. The dose of sympathomimetic drugs may be more important than the route of administration.[5] The mechanisms underlying nocturnal asthma are poorly understood.[6] The most widely accepted view is that it results from the permissive effect on release of mediators from mast cells at night as circulating catecholamine concentrations fall.[7] Sodium cromoglycate might therefore be expected to control nocturnal asthma by stabilising mast cells. Moreover, its low toxicity might facilitate the use of proportionally higher doses than can be contemplated with sympathomimetic drugs. We have studied the effects of sodium cromoglycate, in a standard dosage of 80 mg/day and a high dosage of 280 mg/day, versus placebo in patients with nocturnal asthma that was inadequately controlled by sympathomimetic drugs.

Methods

Patients were recruited who had nocturnal or early morning wheezing on at least three days a week and who showed an early morning fall in peak expiratory flow rate (PEFR) of more than 25% of their highest daily reading, despite treatment with sympathomimetic drugs. Peak flow results during the day were showing no trend to improve or deteriorate at the time of recruitment. Treatment with sympathomimetic drugs was continued unchanged and additional doses of aerosol β_2 stimulant were permitted as required. For two weeks patients kept diary cards of PEFR (best of three attempts) on waking, one hour after waking, at 1600, and at bedtime. They also recorded nocturnal or early morning attacks of wheezing and breathlessness at rest and on exercise (on a scale of 0–3) during the day, and extra doses of β_2 aerosols taken at night and during the day. They continued the study if criteria for variation in PEFR and nocturnal symptoms were satisfied. Trial treatments were given under double blind crossover conditions with randomised treatment order. Treatments were changed every two weeks, when the investigator also reviewed symptoms by a questionnaire and measured forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). In weeks 3 and 4, patients took nebulised sodium cromoglycate 20 mg (2 ml of 1% cromoglycate nebuliser solution), using a Wright nebuliser and electric compressor, on waking, at 1800, and at bedtime and 20 mg by dry powder aerosol from a spinhaler at 1200, or placebo nebuliser solution and capsules. In weeks 4 and 5 they took 80 mg sodium cromoglycate by nebulisation (4 ml of a 2% cromoglycate solution) three times a day and 40 mg by dry powder inhalation at 1200, or corresponding placebos. Weeks 6 and 7 comprised a washout period when sympathomimetic drugs were continued without any trial medication. In weeks 7 and 8 and weeks 9 and 10 patients crossed over to low and high dose regimens of sodium cromoglycate or placebo, depending on the previous randomisation for active or placebo treatment.

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Results

Twenty three patients (12 female; mean age 39.6 years, range 22–66) satisfied entry criteria in the first two weeks and were recruited to the full study. All were taking aerosol salbutamol or terbutaline four times a day. Sixteen patients took oral aminophylline or theophylline, 13 aerosol steroids, and four oral steroids. Six patients were withdrawn before completing the study: four showed poor compliance, one moved from London, and one developed a severe cold that aggravated his asthma.

The table shows mean PEFR from diary cards. The only significant treatment effect was a small improvement in readings one hour after waking (when all patients had taken aerosol β_2 stimulants), seen with both low and high doses of sodium cromoglycate when compared with placebo. The table also shows those variables for which significant treatment effects were demonstrable from diary cards and clinical assessment. High dose (280 mg) sodium cromoglycate produced small improvements over placebo for number of nights of wheeziness per week and breathlessness score during the day. Low dose (80 mg) sodium cromoglycate reduced requirements for extra doses of bronchodilator aerosols both at night and during the day.

One patient had episodes of flushing during treatment with sodium cromoglycate. Other apparent side effects noted by patients were found to be equally frequent during placebo treatments.

Mean peak expiratory flow rate (PEFR) and symptom scores in 23 asthmatic subjects during two week periods of treatment with low and high dose cromoglycate (SCG) and placebo

	Baseline	Low dose		High dose	
		SCG	Placebo	SCG	Placebo
PEFR ($l.min^{-1}$)					
Waking	290	313	296	305	294
1 hour later	365	381*	355	367*	350
1600	348	360	351	366	351
Bedtime	342	358	338	349	342
Symptom scores					
Nights woken per week	3.04	−0.53	0.15	−0.85†	0.12
Breathless on activity‡	0.77	−0.21	−0.08	−0.21†	−0.01
Daytime aerosol§	2.59	−1.61*	−0.83	−1.55	−0.91
Nighttime aerosol§	1.27	−0.49*	−0.09	−0.30	−0.10

*$p < 0.05$ in comparison with placebo by analysis of variance with repeated measures.
†$p < 0.05$, pairwise comparison with placebo at same dose level, Wilcoxon matched pairs signed ranks test.
‡Breathlessness scored on scale 0–3.
§Mean number of extra puffs per day (or night).

Discussion

Benefits from treatment with sodium cromoglycate were small in these patients who were already having regular treatment with sympathomimetic drugs. There was no evidence of improvement in the overnight fall in PEFR but some symptomatic benefit in terms of frequency of nocturnal wheezing and bronchodilator aerosol consumption was seen. There was no evidence of any greater efficacy for the high dose regimen. This may simply mean that sodium cromoglycate is an inappropriate treatment for nocturnal asthma irrespective of dose. It is difficult to nebulise this large dose, however, and patients remarked that inhalation from the nebuliser was time consuming. Thus inhalation of the higher dose may have been incomplete. Use of a larger number of powder aerosol capsules might therefore have been more efficient.

An inpatient study of 160 mg sodium cromoglycate by nebulisation in nocturnal asthma at bedtime[8] showed small improvements over placebo for overnight fall in vital capacity and oxygen saturation but not FEV_1. There was also less sleep disturbance. A comparison of sodium cromoglycate with ketotifen[9] included data on overnight fall in PEFR and showed a very small benefit from cromoglycate by comparison with placebo.

The lack of an appreciable benefit from standard or high doses of sodium cromoglycate in the control of nocturnal asthma does not therefore support the hypothesis that nocturnal release of mediators from mast cells causes nocturnal asthma[7]—with the caveat that the inhibition of mast cell degranulation by cromoglycate that is demonstrable in animal models may not fully account for its clinical effectiveness in asthma.[10] Although sympathomimetic drugs may inhibit mediator release from mast cells, their beneficial effects in nocturnal asthma[3,4] could be explained by their direct action on bronchial smooth muscle alone.

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