

The effect of inhaled and intranasal sodium cromoglycate on symptoms of upper respiratory tract infections

N. ÅBERG, B. ÅBERG and K. ALESTIG*

Department of Paediatrics and *Department of Infectious Diseases, University of Göteborg, East Hospital, Göteborg, Sweden

Summary

Background A well established drug for the treatment of asthma and allergy, sodium cromoglycate, was found in open trials to be useful as a symptomatic treatment for upper respiratory tract infections.

Objective To compare the efficacy of inhaled and intranasal sodium cromoglycate and matching placebos on the symptoms of upper respiratory tract infections.

Methods Adult subjects with symptoms of runny nose, throat pain, or cough for less than 24 h were recruited. They were treated for 7 days using a randomized, double-blind, placebo-controlled, group comparative design. The medication given was: sodium cromoglycate dry powder 20 mg per inhalation in spincaps; sodium cromoglycate aqueous nasal spray delivering 5.2 mg per dose; or matching placebo as dry powder and nasal spray. One spincap and one spray per nostril were taken every 2 h during waking hours on days 1 and 2 and then four times daily on days 3–7. Severity of nine symptoms (general malaise, body aches and pains, chills and shivering, sneezing, nasal running, nasal blocking, sore throat, cough and voice disturbance) was recorded twice daily by subjects on diary cards, using a scale of 0 (absent) to 3 (severe).

Results The study was conducted between February and April 1993. One hundred and eighteen patients aged 21–63 years (mean 41 years) were included. Symptoms resolved faster ($P < 0.001$) and the severity in the last three days of treatment was significantly less in patients treated with sodium cromoglycate than with placebo ($P < 0.05$ -day 5; $P < 0.01$ -day 6; $P < 0.001$ -day 7). Side-effects were local and mild and did not differ between the treatment groups.

Conclusion Sodium cromoglycate administered both by inhalation and intranasally is an effective treatment for the symptoms of upper respiratory tract infection. Its combined safety and efficacy would make it an acceptable form of treatment for these conditions.

Keywords upper respiratory tract infections, drug therapy, adults, sodium cromoglycate

Clinical and Experimental Allergy, Vol. 26, pp. 1045–1050. Submitted 16 January 1995; revised 13 October 1995; accepted 27 October 1995.

Introduction

During the course of frequent upper respiratory tract infections contracted in paediatric practice, one of the authors (N.Å.) first noticed that his own hoarseness appeared to be prevented by inhaled sodium cromoglycate powder when he demonstrated its use to young asthmatics.

Subsequently, sodium cromoglycate seemed to have remarkably good effects on other symptoms of upper respiratory tract infection (URTI) when it was tested in volunteers. We decided to test these effects in a formal, randomized, double-blind, placebo-controlled clinical study within the general population. Sodium cromoglycate is one of the safest drugs available and if a

Correspondence: Dr N. Åberg, Department of Paediatrics, East Hospital, S-416 85 Göteborg, Sweden.

therapeutic benefit in the treatment of URTI could be confirmed, then it would make an acceptable form of treatment for this common but not particularly serious condition in otherwise normal subjects.

Materials and methods

At two Employee Health Clinics in Göteborg, men and women aged 18–64 years with symptoms of sore throat, runny nose or cough which had been present for less than 24 h were invited to attend. At the time of the initial invitation and when the patients booked for their visit large numbers with a history of allergic rhinitis and asthma were excluded.

At the first visit a full clinical history was taken to confirm that their symptoms conformed to those of an upper respiratory tract infection. The following subjects were excluded at the first visit: subjects whose symptoms had been present for longer than 24 h were excluded; subjects with any history of chronic disease from upper or lower airways (including asthma); pregnant and lactating women and patients with any significant chronic disease; subjects who had been given antibiotics during the previous 4 weeks and those receiving any treatment for chronic airways disease, including oral or inhaled corticosteroids, sodium cromoglycate, nedocromil sodium, oral or inhaled bronchodilators, anticholinergics or theophyllines. No other drugs apart from the test treatment and rescue treatment for URTI were allowed during the trial.

The study was fully explained and the treatments to be used described and all subjects signed a form of informed consent. The protocol and the informed consent form were approved by the Ethical Review Committee of the University of Göteborg. Subjects were provided with daily diary cards on which they recorded (morning and evening) the severity of six symptoms related to the upper and lower respiratory tract: sore throat, sneezing, nasal running, nasal blockage, cough and disturbance of voice. They also recorded the severity of three generalised symptoms: general malaise, body aches and pains, and

attacks of chill and shivering. The severity of these symptoms was recorded on a 4-point scale. Also recorded were additional medications taken for URTI and the number of test treatments taken each day. Subjects were randomly assigned to receive either active or placebo treatment in a double-blind manner and asked to return to the clinic 1 week later. At the second visit all diary cards and unused medications were collected and patients were asked about any adverse events which occurred during the treatment, to give an overall opinion as to the efficacy of the treatment received on a 5-point scale (see Table 1) and to guess whether they had received active or placebo treatment.

The active treatment comprised of sodium cromoglycate powder for inhalation and sodium cromoglycate aqueous solution as an intranasal spray. The powder was given in capsule unit doses (Lomudal[®]) each containing 20 mg sodium cromoglycate and inhaled using a turbo-inhaler (Spinhaler). The intranasal solution was 4% concentration (Lomudal Nasal[®]) and each metered dose spray provided 5.2 mg sodium cromoglycate. The contents of one Spinacap were inhaled and one spray was delivered to each nostril every 2 h during the waking hours for the first 2 days and four times a day for the remaining 5 days.

The primary efficacy variables were the severity of the symptoms recorded on the diary cards and the patient's opinion of treatment. For the diary card data the morning and evening symptom scores were averaged to give a single daily value. The first score recorded at the initial clinic visit was used as a baseline value. The symptom scores were therefore reduced to eight values, baseline (B) and days 1–7.

The symptom scores were analysed with parametric tests in two steps. First a two-way (Drug*time) analysis of variance (ANOVA) for repeated measures was applied. If a significant interaction effect was detected the values were analysed with Student's *t*-tests at each time point. The chi-square test or the Fisher's exact test was used to analyse differences in distributions of overall opinion of efficacy, the number of days on which additional medication for URTI was taken, and the number of correct guesses for active or placebo treatment. Probabilities less than the 5% level, using two-tailed tests, were the basis for statistical significance.

Results

The study took place between 4 February 1993 and 16 April 1993. A total of 135 subjects was randomly allocated to test treatment; 17 subjects were not included in the efficacy analysis (13 in the sodium cromoglycate group and four in the placebo group); of these, four

Table 1. Patient's opinion of treatment

Opinion	Sodium cromoglycate		Placebo	
	<i>n</i>	%	<i>n</i>	%
Very effective	16	31%	4	7%
Moderately effective	22	42%	9	15%
Slightly effective	9	17%	16	26%
No effect	5	10%	32	52%
Made condition worse	0	0%	0	0%

Table 2. Patient characteristics

Variable		Sodium cromoglycate group	Placebo group
Number		54	64
Sex: Male		28	33
Female		26	31
Age (years):	Mean	40.9	41.1
	Range	21–63	24–60
Duration of URTI symptoms (hours)	Mean	11.4	11.1
	Range	2–23	1–23
Smoking habits:	Current smoker	8	5
	Former smoker	4	4
	Non-smoker	42	55

did not meet the entry criteria as they were found to have a history of either chronic rhinitis or seasonal allergic rhinitis, five took insufficient medication already on day 1 of the trial, of whom one had a minor adverse reaction to the treatment and five did not comply with the study procedure. A further nine subjects withdrew during the study but were included in the efficacy analysis. Of these nine subjects, six did not complete the treatment period but were included as they took full medication for at least 24 h, one of these had an adverse reaction (sodium cromoglycate). One hundred and eighteen patients were therefore included in the efficacy analysis and their characteristics are shown in Table 2.

The mean daily total scores for the primary efficacy variable, the total symptoms are shown in Fig. 1. The maximum daily total symptom score possible for the nine symptoms is 27. The mean baseline score \pm SEM for the sodium cromoglycate group was 6.28 ± 0.54 (range 1–18) and 5.42 ± 0.36 (range 1–16) for the placebo group. The difference is not significant. The mean scores rose in both groups peaking at 6.80 ± 0.56 on day 1 in the sodium cromoglycate group and at 6.24 ± 0.43 on the same day in the placebo group. Thereafter the symptoms improved in both groups but the range of improvement was significantly faster in the sodium cromoglycate than in the placebo group ($P < 0.001$). The mean daily symptom scores were significantly less in the sodium cromoglycate group on days 5, 6 and 7. Examination of the scores for individual symptoms showed a consistent trend to more rapid improvement in the active group with the greatest effect being seen on cough and voice disturbance ($P < 0.001$ for both).

The other primary variable was the patient's opinion of the efficacy of the treatment received. Five patients (two sodium cromoglycate, three placebo) refused to give an opinion and the distribution of opinion in the five

categories is shown in Table 1. Of subjects who were treated with sodium cromoglycate 73% thought the treatment to be very effective or moderately effective as compared with 22% of patients treated with placebo ($P < 0.001$).

Examination of the total symptom scores on the first 3 days of the study showed that the URTIs could be classified into subgroups according to symptom's severity. The most striking differences between the effects of the two treatments were to be seen in the patients with the most severe symptoms (39 patients with total scores greater than 44 on days 1–3). The scores in the sodium cromoglycate treated sub-group peaked on day 1 at 11.3 ± 0.67 (SEM) and then declined. In the placebo group the symptom scores peaked on day 3 at 11.58 ± 0.89 and then declined. The total symptom scores from

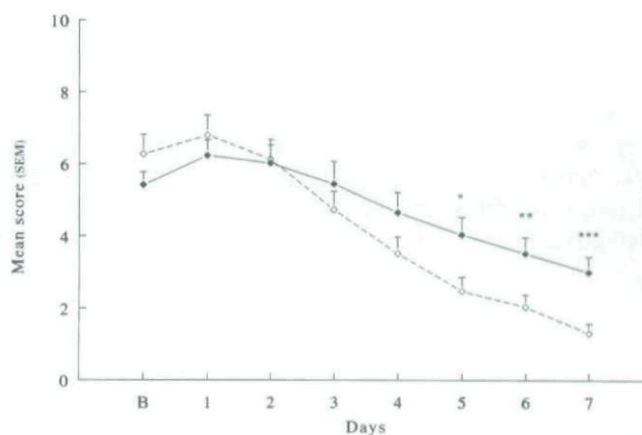


Fig. 1. Effect of sodium cromoglycate and placebo on symptoms of URTI. Mean daily score for all symptoms. \blacklozenge — \blacklozenge , placebo group. \diamond — \diamond , sodium cromoglycate group. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 3. Adverse events

Adverse event	Sodium cromoglycate	Placebo
Coughing (after inhalation)	4	0
Dizziness	1	1
Epistaxis	1	1
Dry mouth	1	1
Sore gums	1	0
Muscle ache	0	1
Muscle tension	1	0
Throat irritation	0	1
Nasal irritation (after spray)	1	3
Stuffy nose	0	1
Bad taste (after inhalation)	4	0
Total	14	9

day 3 to day 7 were significantly lower in the sodium cromoglycate group.

When asked to guess which treatment they had received, of those treated with sodium cromoglycate 31 (57%) guessed it was active treatment, three (6%) guessed placebo and 20 (37%) had no idea; in the placebo-treated group 14 (22%) chose active, 33 (52%) chose placebo and 17 (26%) had no idea. These differences are significant ($P < 0.001$).

Forty-three patients took additional medications for their URTI; 17 in the sodium cromoglycate group and 26 in the placebo group. This difference is not significant. Analgesics/antipyretics was taken by 20 patients in the placebo group and 15 patients in the sodium cromoglycate group for 1–7 days (mean: 2.6 days, placebo; 2.3 days, sodium cromoglycate). Nine patients took nasal decongestants (four active, five placebo), and a further seven patients in the placebo group took either antitussives ($n = 4$) or antibiotics ($n = 3$).

Thirteen patients in the sodium cromoglycate group reported 14 adverse events and eight patients in the placebo group reported nine adverse events. These differences are not significant. Details are shown in Table 3. All adverse events were reported as of mild severity.

Discussion

This trial is the first controlled study of sodium cromoglycate in the treatment of acute viral infections of the upper respiratory tract. The subjects were selected from an otherwise healthy population presenting with symptoms at occupational health clinics. In view of the known effects of the drug in allergic disease or asthma and whilst some of the symptoms could be confused with

exacerbations of an underlying allergic disease or hyper-reactivity in the airways, particular care was taken to exclude all subjects with a history of asthma and allergy at the stage of inviting the public and booking time for the first visit. These efforts resulted in only four patients being randomized who were subsequently found to have a history of allergic rhinitis or chronic rhinitis.

The severity and pattern of viral infections of the upper respiratory tract are best described by combining the severity scores of the individual local and systemic symptoms as has been used in previous research projects on the common cold [1]. The pattern of the acute disease demonstrated in this study follows that expected from previous descriptions. Symptoms increase in severity during the first 48 h and decline thereafter with resolution of the acute illness after 7 days. The effect of sodium cromoglycate when administered to both the upper and lower respiratory tract by intranasal spray and inhaled powder is to reduce the severity and duration of the symptoms.

Sodium cromoglycate is a topically-acting agent with little systemic absorption. It was originally developed for the treatment of asthma when given by inhalation and it is thought to act by preventing the release of chemical mediators of allergic inflammation from sensitized cells in the bronchial mucosa, particularly mast cells [2]. Subsequently it has been administered topically to the nasal mucosa, the conjunctivae and the gastro-intestinal tract for the treatment of allergic rhinitis, allergic conjunctivitis and food allergy. It has always been considered to be a preventive agent with no symptomatic effect. There have, however, been reports that the compound has a bronchodilating effect in some circumstances [3] and animal studies have shown an effect on central and local neurological reflex mechanisms which may be important in producing common cold symptoms [4,5]. In some of his early clinical experiments with inhaled sodium cromoglycate [6], Altounyan showed that the drug enhanced the bronchodilating effect of atropine. An interpretation of this effect is that the drug down-regulates neurological reflexes that have been enhanced in the case of asthma by exposure to antigen. In the present trial it can be argued that the virus infection has up-regulated the normal reflexes that result in nasal secretion, sneezing and coughing and that sodium cromoglycate causes a down-regulation of these reflexes and produces the symptomatic effects observed.

Although the classical mediators of allergic inflammation have not been shown to be important for the inflammatory response to viral infections [7,8], a potent pro-inflammatory cytokine, tumour necrosis factor- α (TNF α) is often present in nasal mucosa in URTI [9] and the release of this mediator from mast cells has been

shown to be inhibited by sodium cromoglycate [10]. The intercellular adhesion molecule ICAM-1 may also play an important role since it is the receptor molecule for rhinovirus [11] as well as being upregulated in inflamed airway epithelium [12] and, experimentally, by $\text{TNF}\alpha$ [13]. Thus, an anti-inflammatory effect at this level may also affect the course of the viral disease.

It is therefore possible that the effect of the drug demonstrated in this study is a combination of the prevention of the local release of mediators from cells damaged by infection and down-regulation of neurological reflexes which have been enhanced in response to infection.

It is known that different viruses differ in the way they activate inflammatory cells in the respiratory mucosa, and also the timing at which this activation takes place, with consequent differences in the timing of the onset of symptoms. It is likely that the patients in this trial had different virological causes for their symptoms and this is an uncontrolled element in the study. As the directional changes favouring active treatment were consistent across all symptom scores and all severity groups, possible differences in the distribution of diseases with varying natural courses between the treatment groups is not considered to have had a major influence on the results.

A protective effect of high concentrations of sodium cromoglycate on the cytotoxic effect of virus infection *in vitro* has been reported but no direct effect on virus has been shown [14,15]. Nedocromil sodium, a compound that is thought to have a similar mode of action to sodium cromoglycate [16], has also been shown to modulate the effects of experimental infection with virus [17]. In these studies there was no effect on the frequency of virus shedding nor on the serological response to the virus, indicating that the effect shown was only to reduce the severity and time course of the symptoms. The effect was significant when the infection was with rhinovirus but less when coronavirus was used. Nedocromil sodium was administered by the intranasal route alone and in order to have a clinically useful effect, as shown in the sodium cromoglycate trial, it may be necessary to administer the drug to the whole of the respiratory tract using both the intranasal and the inhaled routes.

Effective treatment of the common cold has eluded researchers since experiments began. Antiviral treatment with interferon or anti-viral compounds given intranasally have been evaluated in experimental infection [18,19] but their efficacy and safety have not warranted general use. Combination therapy of interferon, ipratropium bromide and naproxen has been reported to be more effective than monotherapy [20]. Blockade of cellular receptors for different infective agents is a new approach that remains to be further developed [21].

In previous drug trials for the treatment of URTI any efficacy shown has been of limited value, particularly in relation to the potential for adverse effects. Sodium cromoglycate differs in that it has an excellent safety profile and record and in this study has been shown to be an effective and clinically useful treatment in limiting the severity and time-course of viral respiratory tract infections. The fact that useful efficacy has been shown when treatment was started after the onset of symptoms makes the drug more suitable for general use in URTI than if prophylactic administration were necessary. The potential use of the drug in URTI particularly in patients with asthma would be an interesting project for future research and may warrant a re-evaluation of this well known drug both within and without its traditional areas of clinical use.

Acknowledgements

We wish to acknowledge the assistance provided by Dr B. Lavenius, Dr S. Raner and the nursing staff at the Employee Health Centre at SKF Tool Ltd and the Bank Health in Göteborg, J. E. Ternström of Fisons Sweden AB and Gunnar Edman of Pons Consulting who conducted the statistical analysis. Test treatments were provided by Fisons Sweden AB who also supported the study.

References

- 1 Beare AS, Reed SE. The study of antiviral compounds in volunteers. In Oxford JS, ed. *Chemoprophylaxis and viral infections of the respiratory tract*. Vol II. Cleveland: CRC Press, 1977: 27–55.
- 2 Orr TSC, Pollard MC, Gwilliam J, Cox JSG. Mode of action of disodium cromoglycate, studies on immediate type hypersensitivity reactions using 'double sensitization' with two antigenically distinct rat reagents. *Clin Exp Immunol* 1970; 7:745–57.
- 3 Chung JTN, Jones BS. Bronchodilator effect of sodium cromoglycate and its clinical implications. *BMJ* 1979; 2: 1033–4.
- 4 Dixon M, Jackson DM, Richards IM. The action of sodium cromoglycate on 'C' fibre endings in the dog lung. *Br J Pharmacol* 1980; 3:180–4.
- 5 Jackson DM, Richards IM. The effects of sodium cromoglycate on histamine reflex bronchoconstriction in the anaesthetised dog. *Br J Pharmacol* 1977; 61:257.
- 6 Altounyan REC. Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease. In: *Disodium Cromoglycate in Allergic Airways Disease* (Pepys J & Frankland AW eds), Butterworths, London, 1970: 47–53.
- 7 Callow KA, Tyrell DAJ, Shaw RJ, Fitzharris P, Wardlaw AJ, Kay AB. Influence of atopy on the clinical manifestations of

- coronavirus infections in adult volunteers. *Clin Allergy* 1988; 18:119–29.
- 8 Eggleston PA, Hendley JO, Gwaltney JM Jr. Mediators of immediate hypersensitivity in nasal secretions during natural colds and rhinovirus infections. *Acta Otolaryngol* 1984; 413 (Suppl): 23–35.
 - 9 Balfour-Lynn IM, Valman HB, Wellings R et al. Tumour necrosis factor- α and leukotriene E_4 production in wheezy infants. *Clin Exp Allergy* 1994; 24:121–6.
 - 10 Bissonette EY, Befus AD. Modulation of mast cell function in the gastrointestinal tract. In: *Immunopharmacology of the gastrointestinal system*. Academic Press, London, 1993: 95–103.
 - 11 Staunton DE, Merluzzi VJ, Rothlein R et al. A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. *Cell* 1989; 56:848–53.
 - 12 Wegner CD, Gundel RH, Reilly P, Hynes N, Letts G, Rothlein R. Intercellular adhesion molecule (ICAM-1) in the pathogenesis of asthma. *Science* 1990; 247:456–9.
 - 13 Dustin ML, Singer KH, Tuck DT, Springer TA. Adhesion of T lymphocytes to epidermal keratinocytes is regulated by IFN γ and is mediated by ICAM-1. *J Exp Med* 1988; 167: 1323–40.
 - 14 Penttinen K, Aarnio A, Hove T. Disodium cromoglycate can inhibit virus-induced cytopathic effects in vitro. *BMJ* 1977; 1:82.
 - 15 Loveday D, Wenham RBM. Effect of disodium cromoglycate on virus-cell system in vitro. *BMJ* 1977; 2:557–8.
 - 16 Orr TSC. Nedocromil sodium: a new therapeutic option for reversible obstructive airways disease. *Br J Clin Pract* 1987; 41(11 Suppl): 9–12.
 - 17 Barrow GI, Higgins PG, Al-Nakib W, Smith AP, Wenham RBM, Tyrell DAJ. The effect of intranasal nedocromil sodium on viral upper respiratory tract infections in human volunteers. *Clin Exp Allergy* 1990; 20:45–51.
 - 18 Del Mar C. Managing upper viral respiratory infections. *Austr Fam Phys* 1990; 20:557–61.
 - 19 Al-Nakib W, Higgins PG, Barrow G et al. Suppression of colds in human volunteers challenged with rhinovirus by a new synthetic drug (R61837). *Antimicrobial Agents and Chemotherapy* 1989; 33:522–5.
 - 20 Gwaltney JM. Combined antiviral and antimediation treatment of rhinovirus colds. *J Infect Dis* 1992; 166:776–82.
 - 21 Hayden FG, Gwaltney JM, Colonno RJ. Modification of experimental rhinovirus colds by receptor blockade. *Antiviral Res* 1988; 9:233–47.

Copyright of Clinical & Experimental Allergy is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.