

The effect of intranasal nedocromil sodium on viral upper respiratory tract infections in human volunteers

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Summary

Two studies involving double-blind group comparative trials in human volunteers compared the effects of intranasal nedocromil sodium (2.6 mg active drug per nostril, q.i.d.) with placebo on clinical symptoms and performance impairment associated with the common cold. In the first study volunteers were challenged with rhinoviruses (RV9 and RV14), and in the second study with respiratory coronavirus. In both studies, active and placebo groups of volunteers were demographically similar. Infection rates in both groups were also similar. There were no withdrawals resulting from unusual symptoms related to either treatment. In the rhinovirus study (19, placebo; 20, nedocromil sodium) daily symptom scores and daily mean nasal secretion weights were significantly lower in the nedocromil sodium-treated group. In the coronavirus study (26, placebo; 27, nedocromil sodium) there was little difference in the severity of colds between the active and placebo-treated groups, but trends favoured nedocromil sodium. In both studies the impairment of performance in volunteers who developed a cold was significantly less in those treated with nedocromil sodium than in those treated with placebo.

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Introduction

Topical nedocromil sodium has been shown to be of benefit in the prevention and treatment of asthma in man [1]. This compound, the disodium salt of a pyranoquinoline dicarboxylic acid, inhibits the immediate and late asthmatic reactions [2] resulting from antigen challenge to the lung and also prevents bronchoconstriction caused by exercise [3] and SO₂ inhalation [4]. Furthermore, it reduces seasonal bronchial hyperresponsiveness in pollen-sensitive subjects [5]. Nedocromil sodium has also been shown to reduce rhinitis induced by experimental antigen challenge, and in clinical trials is effective in the treatment of seasonal allergic rhinitis [6].

Nedocromil sodium stabilizes both mucosal and connective tissue mast cells, alveolar macrophages and basophils and it may improve asthma by suppressing the release of mediators such as histamine, leukotriene C₄ and prostaglandin D₂ [7]. Attempts to show, by direct measurement, that histamine or leukotrienes are respon-

sible for part or all of the inflammatory response to viral infection of the upper respiratory tract have been unsuccessful or at best inconclusive [8-10]. The aim of the present studies was to investigate the effect of nedocromil sodium on symptoms resulting from infection with two different respiratory viruses. A beneficial effect in either or both infections would provide indirect evidence that one or more of the mediators suppressed by nedocromil sodium plays a part in the symptomatology of the common cold caused by either rhinovirus, type 9 (RV9) and type 14 (RV14), or a coronavirus, 229E.

It has also been shown that colds may impair the efficiency of human performance [11]. It is important, therefore, to examine whether nedocromil sodium not only changes clinical symptoms but also reduces the performance impairments associated with having a cold.

Subjects and methods

Study design

Both studies were approved by the Harrow District Ethical Committee at Northwick Park Hospital and were performed according to similar protocols.

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Healthy volunteers of either sex between the ages of 18 and 50 years without known allergic disease were recruited and housed in isolation in groups of two or three according to the normal practice at the MRC Common Cold Unit, Salisbury [12,13]. All volunteers completed a questionnaire to assess their introversion/extroversion and certain obsessional factors as these have been shown to influence the outcome of virus challenge [14].

Blood samples were collected from each subject on arrival for full haematological screening and biochemical examination, including electrolytes, renal and liver function tests. After a 2-day quarantine period, subjects were assigned randomly by number in sequence to active or placebo treatment groups; the code was not broken until all clinical and virological data had been reported. Medication consisted of one spray to each nostril four times a day under supervision (at 8 a.m., 1 p.m., 6 p.m. and 10.30 p.m.) for 7 days. One hour after the fifth dose of medication, volunteers received nasal drops containing the challenge virus. For rhinovirus the nasal challenge contained an estimated 100 TCID₅₀ of human RV9 followed by a similar inoculum of RV14 1 hr later. For coronavirus, the single challenge dose was approximately 750 TCID₅₀ of a strain of 229E. In both studies a small number of volunteers were given saline instead of virus, thus providing information on tolerance to the drug as well as maintaining the double-blind nature of the trial.

Each volunteer was assessed daily by a clinician who, like the subjects, was unaware of the nature of the challenge and of the medication received. The signs and symptoms were recorded, together with the number of paper tissues used in the previous 24 hr. After single use, paper tissues were sealed in plastic bags (five tissues per bag) and weighed to determine the amount of nasal secretion produced each day. At the end of the trial the clinical observer scored all the signs and symptoms as well as the number of paper tissues used (less the average before challenge) according to a standard protocol, to give a daily and total score [12] for each volunteer. From these daily and total scores for each volunteer the mean daily and mean total scores were calculated for the drug and placebo groups. A clinical assessment as to whether the volunteer had suffered no cold, a doubtful cold (not clinically significant), or a significant cold of a mild, moderate or severe grade was made [15]. Blood samples for repeat haematological and biochemical tests were collected at the end of medication and another was requested 2 weeks later for antibody assay.

Medication

Nedocromil sodium in an isotonic solution containing 0.715% (w/v) sodium chloride, 0.01% (w/v) disodium

edetate and 0.01% (w/v) benzalkonium chloride was dispensed as a nasal spray which delivered 0.13 ml per activation (1.3 mg of nedocromil sodium). The placebo, which contained 0.0005% (w/v) riboflavin, 0.9% (w/v) sodium chloride, 0.01% (w/v) disodium edetate and 0.01% (w/v) benzalkonium chloride, was dispensed as a similar spray delivering 0.65 µg of riboflavin per activation. Both nedocromil sodium and placebo were prepared and coded by Fisons plc, Pharmaceutical Division.

Virological procedures

Nasal washings were collected from each volunteer prior to inoculation and daily from day 2 to day 6 inclusive after inoculation; they were mixed with an equal volume of nutrient broth and stored at -70°C.

Rhinovirus types 9 and 14. The presence of virus was determined by the cytopathic effect in roller tube cultures of Ohio HeLa cells inoculated with nasal washings. At least one isolate from each subject was shown by neutralization tests to be of the same serotype as one of the two challenge viruses. Serum neutralizing antibody titres were assayed by a micro-neutralization test and a fourfold or greater rise was taken as evidence of infection.

Coronavirus. The presence of virus and confirmation that it was the same as that used for challenge was determined by the characteristic cytopathic effect produced in C16 cells. The concentration of serum antibody following challenge was assayed by an ELISA test and measured in arbitrary units by comparison with a standard serum. An increase of 10^{0.14} units (or greater) in the convalescent serum compared with the pre-challenge serum was taken as evidence of infection.

Performance test procedures

Each volunteer was tested once in the pre-challenge period and once when symptoms were observed, usually between days 6 and 9.

The tests used were two choice reaction time tasks developed by Broadbent [14]; performance of these has been shown to be impaired by colds [16]. Subjects carried out 320 trials in each task.

Statistical methods

The clinical and virological data were analysed using the Mann-Whitney *U*-test and Fischer's exact test with a significance level of 5%. Data tested by the former were also analysed using the Mack-Skilling statistic which

Table 1. Rhinovirus trials

Volunteer group	Pre-trial antibody titre*	Number	No. with significant colds	Antibody rise	Virus	Either/both
Nedocromil sodium	<2	17	9	15	16	17
	2-4	1	1	1	1	1
	>4	2	0	2	2	2
Total		20†	10	18	19	20
Placebo	<2	16	12	10	14	14
	2-4	2	1	0	1	1
	>4	1	0	1	1	1
Total		19‡	13	11§	16	16

* Given as the reciprocal of the end-point dilution.

† Males 10, females 10. Mean age 33.80 ± 9.9 yr. Introversion/extroversion score 10.95; obsessional score 1.26.

‡ Males 10, females 9. Mean age 31.58 ± 8.8 yr. Introversion/extroversion score 11.58; obsessional score 2.74.

§ Eighteen paired sera tested.

examines differences after adjusting for a blocking factor. In these studies the blocking factor was the pre-study antibody levels, which were split into three strata.

With the performance test data, analyses of covariance were performed with the pre-challenge scores as the covariate. This statistical technique takes account of baseline differences when assessing the effect of illness and drug.

Results

Rhinovirus trials

Fifty-five volunteers attended three trials. Ten volunteers were excluded, either because of wild colds or contact with one (7) or because of abnormal results in haematological or biochemical tests (3). A further two were unable to complete the trial, one because of an accident and one for social reasons. Of the remainder, 39 were inoculated with viruses and four with saline.

Saline recipients. Three volunteers received placebo and one volunteer received nedocromil sodium. Three of the four were recorded as suffering no cold (mean total score = 2). The fourth volunteer, given placebo, had a mild cold (score = 12) and virus was detected in nasal washings on days 3 and 6 after challenge. This infection was presumably acquired from a flat-mate who had been experimentally infected, developed a cold and excreted virus on all of the 5 days post-challenge that washings were collected.

Virus recipients. Of the 39 volunteers inoculated with virus, 20 received nedocromil sodium and 19 were given placebo. The two groups were well-balanced for age, sex, pre-trial antibody titres and introversion/extroversion scores, but the score for obsessional factors was significantly higher ($P < 0.01$) in the placebo group (Table 1). All the volunteers given drug (20) showed evidence of infection as did 16 of the 19 given placebo. Ten (50%) of those given drug suffered clinically significant colds compared with 13 of the 19 (68%) receiving placebo.

Comparing only volunteers who had evidence of infection, as determined by virus isolation or antibody rise, there was a consistent trend that those receiving nedocromil sodium had fewer and/or milder symptoms, although there was no significant difference in the overall severity of the colds in the two groups as judged by the clinical grading: eight mild, one moderate, one severe in the nedocromil sodium group, compared with 11 mild and two moderate in the placebo group. However, four doubtful colds (i.e. symptoms not sufficiently severe or persistent to enable a firm diagnosis of a cold to be made) occurred in the active drug group but only one in the placebo group. Thus, 14 of the 20 infected volunteers given drug had upper respiratory symptoms compared with 14 of the 16 volunteers receiving placebo. Furthermore, both the mean daily clinical scores and the mean daily nasal secretion weights were lower in the treated than in the placebo group (Fig. 1). The mean total clinical score for the nedocromil sodium group was 12 compared with 17 in the placebo group, and the corresponding

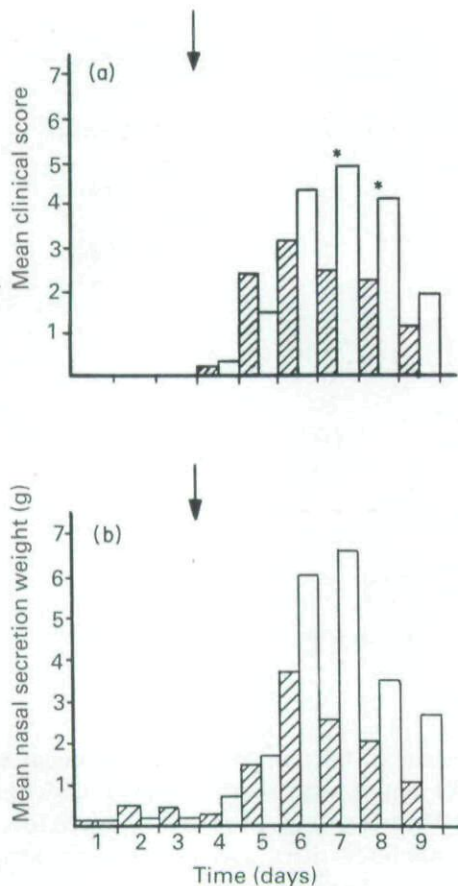


Fig. 1. Mean daily clinical scores (a) and mean daily nasal secretion weights (b), recorded in the rhinovirus trials for infected volunteers only, plotted against time. The arrow indicates the point of virus challenge. (▨), Nedocromil sodium, and (□), the placebo groups. * $P < 0.05$.

values for the mean total nasal secretion weights were 11 g and 21 g. A statistically significant difference between the two groups was shown by the mean clinical scores on days 7 and 8 ($P < 0.05$).

The results from the performance tests were similar in both the rhinovirus and coronavirus trials and they are summarized at the end of the results section of the coronavirus trial.

Coronavirus trials

Sixty-three volunteers attending five trials took part in the study. One volunteer was excluded because of hay fever and another because of abnormal haematological and biochemical tests results; family illness prevented one volunteer from completing the trial and another volunteer was excluded retrospectively as virus was present in the pre-challenge nasal wash. Of the remainder, 53 were challenged with virus and six with saline.

Saline recipients. Four volunteers received placebo and two received nedocromil sodium. No illness was experienced by any volunteer and the mean total clinical score for those receiving nedocromil sodium was 1.5 compared with 2.25 for those given placebo.

Virus recipients. Twenty-seven of the 53 volunteers challenged with virus received nedocromil sodium; 26 were given placebo. All but one (given nedocromil sodium) were female and the two groups were well-balanced for age and pre-trial antibody titres. The scores for both obsessional factors and extroversion were higher in the placebo than the drug group but this did not reach statistical significance (Table 2). Laboratory evidence of infection was obtained in 20 (74.1%) of the 27 volunteers given drug and in 22 (84.6%) of the 26 receiving placebo. Nine (33.3%) of the 27 volunteers given drug and 12 (46.2%) of those receiving placebo suffered clinically significant colds. If doubtful colds are also included then there were 16 volunteers with upper respiratory symptoms in each group. There was little clinical difference in the severity of the colds in the two groups: two moderate, seven mild and seven doubtful in the nedocromil sodium group compared with two moderate, 10 mild and four doubtful in the placebo group.

Among the infected volunteers there is no direct relationship between mean daily clinical scores or mean daily nasal secretion weights and medication (Fig. 2). However, the mean total clinical score in the placebo group (16.3) was higher than that of the drug group (14.78). The reverse is true for the mean total nasal secretion weight: 18.45 g in the nedocromil sodium group and 10.82 g in the placebo group. In clinical observations the only statistically significant difference ($P < 0.05$) demonstrated was for nasal secretion weight on day 9.

The results of the performance tests were similar in both the rhinovirus and coronavirus trials. The mean reaction times for the different conditions are shown in Table 3. In subjects given nedocromil sodium and clinically assessed as having colds, impairment of performance was less than in those subjects given placebo. However, in subjects receiving nedocromil sodium but with no evidence of a cold, reaction times were increased. This resulted in a significant interaction ($P < 0.05$) between colds/no colds and drug/placebo conditions.

Discussion

Intranasal nedocromil sodium appeared to be well tolerated, and in those volunteers receiving nedocromil sodium without virus challenge, there was no evidence of local irritation. Haematological and biochemical tests performed before and after treatment were within normal

Table 2. Coronavirus trials

Volunteer group	Pre-trial antibody titre (units)	Number	No. with significant colds	Antibody rise	Virus	Either/both
Nedocromil sodium	< 10 ³	9	5	8	6	8
	10 ^{3.5}	13	4	7	7	8
	> 10 ^{3.5}	5	0	2	3	4
Total		27*	9	17†	16	20
Placebo	< 10 ³	12	8	11	11	12
	10 ^{3.5}	10	3	3	6	6
	> 10 ^{3.5}	4	1	3	4	4
Total		26‡	12	17§	21	22

* Males 1, females 26. Mean age 35.2 ± 10.4 yr. Introversion/extroversion score 8.74 ± 5.14, obsessional score 2.22 ± 1.87.

† 25 sera examined.

‡ Females 26. Mean age 34.9 ± 11.5 yr. Introversion/extroversion score 10.42 ± 5.26, obsessional score 2.92 ± 1.85.

§ 24 sera examined.

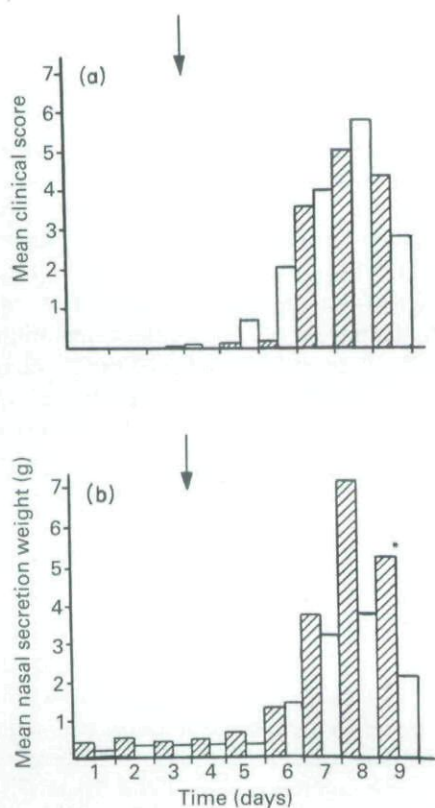


Fig. 2. Mean daily clinical scores (a) and mean daily nasal secretion weights (b), recorded in coronavirus trials for infected volunteers only, plotted against time. (▨) Nedocromil sodium, and (□) placebo groups. **P* < 0.05.

Table 3. Mean reaction times (msec) for volunteers with and without colds who were given placebo or nedocromil sodium

Trial	Colds		No colds	
	Nedocromil sodium	Placebo	Nedocromil sodium	Placebo
Rhinovirus	451	493	485	464
Coronavirus	467	486	493	472

limits and were not significantly different from those receiving placebo.

Treatment with nedocromil sodium had no effect on the frequency of virus shedding in either study nor on the serological response to the virus. This was expected because nedocromil sodium was shown in this laboratory to have no antiviral activity against rhinoviruses 9 and 14 in tissue culture.

In the rhinovirus trial it is possible that the imbalance in obsessional symptom scores between the two groups (Table 1) rather than the drug itself could account for the differences in mean clinical score and mean nasal secretion weights [14]. However, in this study there was no correlation between obsessional score and nasal secretion weight or clinical score when all volunteers were included; a negative correlation was demonstrated for volunteers within the placebo group. Therefore it is concluded that

the reduced mean daily clinical scores and secretion weights were attributable to the action of nedocromil sodium. If this is correct then some colds which would have been classified as significant without drug might be assessed as doubtful colds when the drug is given. In the rhinovirus trial 13 (81%) of the 16 infected subjects who received placebo developed significant colds compared with only 10 (50%) of those given drug. However, if doubtful colds are included, 87.5% of placebo recipients had symptoms compared with 70% of those given drug. By the same reasoning it could be argued that the remaining difference could be accounted for by nedocromil sodium suppressing symptoms to the extent that, what would have been diagnosed as doubtful colds were recorded as no cold.

In the coronavirus study fewer volunteers (42 of 53: 79.3%) showed evidence of infection than those in the rhinovirus trials (92.3%). Of those given nedocromil sodium only nine (33.3%) compared with 12 (46.2%) receiving placebo suffered a clinically significant cold. However, as in the rhinovirus trials, if doubtful colds are included 16 volunteers in each group had upper respiratory symptoms. There was little difference in the mean clinical scores between the treatment groups despite the differences in nasal secretion weights. Increased nasal secretion is reflected in increased use of paper tissues and the later contributes heavily to the clinical score. In the coronavirus trial, although the mean total nasal secretion weight was greater in the nedocromil sodium group than in the placebo group there was no corresponding increase in the mean total clinical score, thus suggesting that nedocromil sodium reduced those symptoms of a cold other than nasal secretion.

The results of these studies suggest that nedocromil sodium partially prevents some of the symptoms of a cold caused by rhinoviruses and to a lesser extent coronaviruses and that the mediators suppressed by this drug have a role in the symptomatology of such colds [10].

There are differences in rhinovirus and coronavirus infections: the incubation period leading to the appearance of symptoms is longer for coronavirus. Clinically, the amount of nasal secretions is the main feature distinguishing coronavirus from rhinovirus colds. This suggests that the mechanism by which nasal secretion is stimulated differs and could account for the different response to the drug in the two types of infection. It is possible, however, that nedocromil sodium did not block mediator release entirely so that the symptoms and signs of infection were not completely suppressed. This is analogous to the break-through of symptoms which may occur during treatment of seasonal allergic rhinitis [17].

Included in these studies were measurements on performance changes in the subjects. It is reported elsewhere

how minor respiratory infections are associated with measureable and substantial declines in human performance and that the decline is specific, for example, colds impair performance in tasks measuring hand/eye co-ordination but not those requiring attention [11,18]. In both these trials, nedocromil sodium prevented loss of performance in subjects suffering clinical symptoms of colds, although the explanation for this is not known. Volunteers who were given the drug but did not develop a cold showed slower performance than those without a cold who had been given the placebo. At the moment it is unclear exactly what is responsible for this effect. In the rhinovirus trial there were more volunteers with sub-clinical infections in the drug group compared to the placebo group. Previous studies have shown that even sub-clinical infections may impair performance [19] and this could be one of the factors contributing to the slower response times in the no colds/drug group.

Viral infections of the upper respiratory tract precipitate exacerbations of asthma and increase airway responsiveness in asthmatic patients [20] as well as in normal subjects [21], although this finding is questioned by others [22]. Nedocromil sodium inhibits the release of mediators from inflammatory cells and reduces inflammation of the airways associated with asthma [23]. Could similar mechanisms account for the beneficial effect, shown here, of nedocromil sodium on the symptomatology of experimental colds? The recent study reported by the Common Cold Unit failed to show raised levels of LTB_4 and LTC_4 or histamine [8], mediators which have been implicated in asthma, in the nasal secretions of subjects following viral inoculation. However, the inability to detect these mediators by direct methods does not exclude them from playing a role, albeit minor, in the common cold. Present knowledge of the mode of action of nedocromil together with the reduction we observed in the symptomatology of rhinovirus and coronavirus infections in volunteers given this compound suggest that such mediators may be responsible for some of the symptoms in upper respiratory viral infections.

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