Nedocromil and Exercise-Induced Asthma: Acute and Chronic Effects

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Abstract

Background: Nedocromil sodium confers both acute and chronic protective effects in patients with bronchial asthma, the interactions of which are unknown.

Objective: To examine to what extent and for how long nedocromil sodium prevents exercise-induced asthma when given immediately before exertion compared to chronic administration.

Patients and Methods: Eighteen asthmatic patients were given 4 mg NS at 30 min or 3.5 hours before exertion. We compared the resultant effect with that of the same protocol measured after 2 and 4 weeks of continuous treatment with the drug.

Results: Nedocromil sodium decreased exercise-induced asthma similarly at both points when given acutely. Chronic treatment of up to 4 weeks did not improve this protective effect at either interval following the inhalation.

Conclusion: Nedocromil sodium most likely reaches its maximal effect on exercise-induced asthma upon the first administration, although treatment for longer than 4 weeks might be required to prove a chronic effect of the drug.

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Nedocromil sodium, a pyranoquanoline dicarboxylic acid, was found *in vitro* [1] and *in vivo* [2] to have mast cell-stabilizing properties, as well as the capacity to prevent eosinophil infiltration in the lung of guinea pigs following allergen inhalation [3]. It also modulated bronchoconstriction in these animals by effecting the non-adrenergic non-cholinergic system [4].

In asthmatic patients, the drug was found to provide protection against allergen, sulfur dioxide, fog, cold air, and exercise-induced asthma [5–9], and the administration twice daily of 4 mg NS[1] aerosol controlled their symptoms and improved their lung function [10,11]. Several *in vivo* studies have shown the particular efficacy of this drug in diminishing the late-phase asthmatic response [6,12]. Thus, it can be concluded that NS has both an immediate protective action, as seen from its effect on EIA[2], and a delayed effect on inflammation which becomes apparent after several weeks of treatment. Speculating that prolonged (chronic) treatment with NS prevents EIA more effectively than when given acutely, we examined the effect of chronic daily regimens of NS on the protection afforded against EIA.

Patients and Methods

Patients

The study group comprised 21 asthmatic patients with previously documented EIA and a drop of at least 20% of forced expiratory volume in 1 sec following exercise. There were 13 males and 8 females with a mean age of 22 years (range 17–25 years).

The mean baseline forced vital capacity of the group was 98% (±2 SD = 8%)(of the predicted value) and the mean baseline FEV_1[3] was 76%. All the patients had a baseline FEV_1 of not less than 70% (±2 SD = 7%) of the predicted value.

Patients taking cromolyn sodium or inhaling with bronchodilators discontinued their use for 24 hours prior to the study, while long-acting theophylline was stopped 48 h before the study. None of the patients was taking steroids of any type, and all were in remission at the time of the study. All the patients gave written informed consent to participate in this research, which was approved by the Hospital Ethics Committee

Methods

All spirometric tests, performed with a Fukuda Spiroanalyzer (CSA 800, Japan), commenced at 8 a.m. The FVC[4] maneuver was performed at least three times in the sitting position, until a deviation of the sum of FEV_1 and FVC was less than 5% in three curves. Only the best curve was used for further analysis. The exercise test consisted of steady-state running on a treadmill (Quinton, USA) for 10 min, maintaining a heart rate of 85% of the maximum predicted value. The same workload was repeated for each test in individual patients. The room temperature during exercise was kept at 22–25°C, and the relative humidity

[1] NS = nedocromil sodium

[2] EIA = exercise-induced asthma

[3] FEV_1 = forced expiratory volume in 1 sec

[4] FVC = forced vital capacity

remained between 50 and 70%. Spirometry was done at baseline, at 30 min after administration of the drug and the placebo inhalation, and again at 5, 10, 15, 20 and 30 min after completion of the exercise test. The lowest value of FEV_1 was used to calculate the change following exercise (baseline value being the lowest value following exercise), and the response to the treatment was expressed as percentage protection. At 3.5 h following the inhalation, the same procedure was repeated, with spirometry again being performed at baseline and following exercise.

The two study days were separated by a period of one week. A variability in baseline FEV_1 of less than 10% was allowed. During phase I of the study, the acute effect on EIA of blindly inhaling either 4 mg NS or a placebo was examined in a double-blind crossover manner. During phase II, marked by the completion of phase I, the patients randomly inhaled either 4 mg NS or placebo twice daily for a period of 2 weeks, also in a double-blind crossover design. The effect of 4 mg NS on EIA was again evaluated in the manner described for phase I. Nine of the patients who completed the 2 week trial continued inhaling NS for another 2 weeks (a total of 4 weeks), after which the effect of NS on EIA was again tested at 30 min and 3.5 hours.

Analyses

For phase I, a repeated analysis of variance (ANOVA) with two factors (treatment and challenge) was carried out. For the chronic phase, ANOVA with challenge day and challenge time was carried out at 2 and at 4 weeks.

Results

Eighteen patients completed phase I and were included in the analysis. Three patients did not perform the pulmonary function test accurately and were excluded. There was no significant change in FEV_1 following placebo or NS both at 30 min and at 3.5 hours (prior to exercise). The maximal drop in FEV_1 seen following exercise was observed at 5–10 min thereafter. As seen in Table 1, there was a significant difference between treatment in favor of NS ($P<0.001$) at 30 min and at 3.5 hours. Following NS, the mean drop in FEV_1 after the first exercise was insignificantly smaller than the one at 3.5 hours.

Thirteen patients completed the chronic phase I (2 weeks) and were included in the analysis; the remaining 5 were not included due to poor compliance. The difference in baseline FEV_1 after 2 weeks of NS inhalation from baseline values was not significant compared to placebo. Initially, ANOVA assessment with the challenge day and challenge time showed a highly significant difference between challenge days ($P<0.001$), as well as a significant interaction between the two factors ($P<0.05$). The mean maximum percentage changes in FEV_1 are shown in Table 2. When a separate analysis of each challenge was performed, a highly significant ($P<0.001$) difference was found between the four treatment regimes at 30 min. In particular, the results of the three NS regimes revealed that NS used for pretreatment gave better protection than the regime in which a placebo was given prior to treatment. There was no significant difference between the challenges at 30 min among the acute and chronic groups.

The results at 3.5 h were less statistically significant. These findings showed that the regime with placebo given as pretreatment provided significantly poorer protection than the NS regime, as well as regimes with NS given as pretreatment in the acute phase and those with NS given chronically.

There does not appear to be any evidence of increased protection after chronic NS treatment for 2 weeks, either at 30 min or at 3.5 h. Nine of the patients who completed 2 weeks of treatment continued inhaling NS for an additional 2 weeks, and the effect on EIA was again compared with that of a placebo at 30 min and at 3.5 h after inhaling the drug. Baseline FEV_1 after 4 weeks of NS inhalation did not show a significant change compared to that measured at baseline and following 2 weeks of treatment with the

Table 1. Overall analysis (n=18) of acute phase: maximum percentage fall in FEV_1

	Challenge at	
	30 min	3.5 h
Nedocromil sodium	16.2	13.2
Placebo	28.7	23.6
SD	6.81	
Effects (*P* value)		
Treatment	$P<0.001$	
Challenge	$P<0.005$	
Treatment x challenge	$P<0.4$	

SD = standard deviation

Table 2. Overall analysis (n=13) of chronic phase (2 weeks): maximum percentage fall in FEV_1

		Challenge at	
Phase	Pretreatment	30 min	3.5 h
Acute	NS	15.2	13.0
Acute	Placebo	29.7	23.3
Chronic	NS	12.2	16.2
Chronic	Placebo	17.7	21.0
SD		8.27	
Effects (*P* value)			
Treatment		$P<0.001$	
Challenge		$P<0.50$	
Treatment and challenge		$P<0.10$	

Acute refers to the pretreatment analysis for the 13 patients only who completed the 2 weeks treatment.

Table 3. Chronic phase (4 weeks): maximum percentage fall in FEV_1

		Challenge at	
Phase	Pretreatment	30 min	3.5 h
Acute	NS	11.1	9.0
Acute	Placebo	28.2	29.9
Chronic	NS	8.2	9.3
Chronic	Placebo	20.3	18.1
SD		7.2	8.3
Significance		$P<0.01$	$P<0.05$

Acute refers to the pretreatment analysis for the 9 patients who completed the 4 weeks of treatment.

at baseline and following 2 weeks of treatment with the drug. The protection provided by NS inhalation was again seen at both time points [Table 3], and again there was no evidence of increased protection after 4 weeks of NS treatment. The pretreatment protection shown for the 13 patients in Table 2 and the 9 patients in Table 3 is indicated as an acute protection.

Discussion

The results of this study confirm the findings of other investigators that NS partially prevents both at 30 min and at 3.5 hours. In addition, there was no additional protective effect when NS was given daily for either 2 or 4 weeks. Thus far, it has been demonstrated that NS not only provides an immediate protective effect [5–9], but also has anti-inflammatory properties.

Despite the vast amount of information available in the literature [2–4], the exact modes of action of this drug are not altogether clear. However, its modulating effect on the non-adrenergic non-cholinergic system [9] can, at least, explain how NS prevents EIA. NS seems to reduce inflammation by stabilizing the mast cells [2], preventing eosinophil infiltration into the lung [3], or by effecting T cell function [4]. Chronic treatment with NS has been reported to diminish bronchial hyper-reactivity to methacholine after 8 weeks, probably by affecting inflammation [13]. Consequently, we expected that chronic treatment with NS would prevent EIA or prolong the drug's action. The fact that this regimen provided no greater preventive effect on EIA seems to indicate that acute and chronic effects are independent of each other. Furthermore, it is also possible that the improved bronchial hyper-reactivity following chronic treatment with NS is too small to have an effect on EIA. Indeed, in the study by Bel et al. [13], bronchial hyper-reactivity decreased significantly only at 8 weeks — and not before, as measured in the current study. Prolonged treatment with NS is probably required for EIA to be significantly affected. In contrast, inhaled budesinide was shown by Henriksen and Dahl [14] to diminish EIA after 4 weeks of treatment. This is possible since inhaled steroids have a more potent effect on asthmatic patients. A higher dose of nedocromil or longer duration of treatment will probably demonstrate the desired protection.

We conclude that NS most likely reaches its maximal effect in preventing EIA when given on the first occasion, similarly at both 30 min and 3.5 hours, and that 2–4 weeks of treatment does not significantly enhance its effect. Longer treatment might be required to demonstrate an additional protective effect beyond the initial one.

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I wasn't driven into medicine by a social conscience but by rampant curiosity.

Jonathan Miller (1934–), British psychologist, actor, and director, 1983.
The Observer (February 5, 1983).