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Dose duration of nebulized nedocromil sodium in exercise-induced asthma

M.K. Albazzaz*, M.G. Neale**, K.R. Patel*

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ABSTRACT: The dose-duration effect of nebulized nedocromil sodium was studied in ten patients with exercise-induced asthma (7 males mean (SEM) age 30.1 (3.5) yrs and predicted forced expiratory volume in one second (FEV_1) 102%). All of these patients showed >40% protection of their exercise asthma with 4 mg of nedocromil sodium delivered *via* metered dose inhaler.

Three concentrations of nedocromil sodium (0.5, 2.5 and 10 mg·ml^{-1}) and placebo were administered in double-blind, randomized manner. One ml of each solution was nebulized *via* a Wright nebulizer. Effects were assessed from the mean maximal percentage fall in FEV_1 after 6–8 min treadmill exercise at 15, 135 and 255 min following each treatment and expressed as percentage protection.

The mean baseline FEV_1 values before and after treatments were comparable on four days of testing. Nedocromil sodium inhibited exercise-induced fall in FEV_1 at all concentrations ($p<0.001$) and the inhibitory effect was still present at 255 min. No differences were observed between active treatments.

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* Dept of Respiratory Medicine, Western Infirmary, Glasgow, UK. ** Fisons PLC, Loughborough, Leicestershire, UK.

Correspondence: K.R. Patel
Dept of Respiratory Medicine
Western Infirmary
Glasgow
G11 6NT
UK

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Nedocromil sodium is a pyranoquinoline dicarboxylic acid which exhibits mast cell stabilizing properties, and has been developed for the treatment of reversible airways disease [1]. It prevents histamine release from lung mast cells [2] and in asthmatic patients nedocromil sodium aerosol (4 mg) is effective in blocking allergen-induced bronchoconstriction for up to 3 h [3]. This drug also offers protection in sulphur dioxide, fog, cold air and exercise-induced asthma [4]. In clinical trials, 4 mg of nedocromil sodium aerosol given twice daily was found to be more effective than placebo in controlling symptoms and improving lung function in adult asthmatic patients [5]. We have previously shown that nebulized nedocromil sodium, in concentrations of 0.5–20 mg·ml^{-1} (1 ml of solution), is effective in inhibiting exercise-induced asthma [6]. Little is known of the dose-duration effect of nedocromil sodium in different bronchial provocation challenges. In this study, we have examined the dose-duration effect of nedocromil sodium in patients with exercise-induced asthma using a nebulized solution of different concentrations to allow flexibility in dosing.

Patients and methods

Ten patients (7 males) with extrinsic asthma, mean (SEM) age 30.1 (3.5) yrs and mean predicted forced expiratory volume in one second (FEV_1) 102% were enrolled. The study was approved by the Hospital Ethics Committee and informed consent was obtained from each patient. Patients taking sodium cromoglycate and inhaled bronchodilator discontinued these for 24 h and 12 h, respectively, before each test. Inhaled corticosteroids were continued during the study. None of the patients was taking oral steroids, theophylline preparations or antihistamines. All patients had previously been shown to have both exercise-induced asthma with a fall in FEV_1 of >20% after exercise and at least 40% protection of their exercise-induced asthma with 4 mg of nedocromil sodium aerosol. FEV_1 was measured using a dry-wedge spirometer (Vitalograph, Buckingham, UK) and the best of three attempts recorded for analysis.

The exercise test consisted of steady-state running on an inclined treadmill for 6–8 min at submaximal workload. The same setting and duration were used for each test in any one patient. The study in each patient was completed within 15 days. The temperature on exercise days was maintained between 20–22°C and the relative humidity between 40–60%.

The effect of inhaling nedocromil sodium aerosol (4 mg) was studied first. The second part of the study was carried out in a double-blind, random order (4×4 Latin square) using nedocromil sodium solution in varying concentrations (0.5, 2.5 and 10 mg·ml^{-1}) and placebo. The drugs were delivered through a Wright nebulizer driven by compressed air at a flow rate of 9 *l*·min^{-1} (18 psi). All inhalations were carried out at tidal breathing until 1 ml of the solution was nebulized.

The calculated doses of nedocromil sodium absorbed from the lung were 0.03 mg from 0.5 mg·ml^{-1}, 0.13 mg from 2.5 mg·ml^{-1} and 0.5 mg from 10 mg·ml^{-1} (based on our pharmacokinetic data published previously [6]). The FEV_1 was recorded before and immediately after inhalation, 15 min after inhalation (pre-exercise) and then at 1, 2, 5, 10, 15 and 30 min after exercise. The exercise in each patient was repeated 135 and 255 min after treatment at identical workload.

The FEV_1 response to exercise was expressed as the maximal fall in FEV_1 from the post-drug baseline at 15 min and response to active treatment was expressed as percentage protection (% fall on placebo minus % fall on active treatment divided by fall in placebo × 100). Responses to each concentration were compared by a two-way analysis of variance and Student's t-test, pairwise comparisons being made using Duncan's multiple range test, with a probability level of 0.05.

Results

There was no significant difference between the mean values of FEV_1 before and after inhalation of placebo and nedocromil sodium on 4 days of exercise testing. Similarly the mean (SEM) relative humidity was also comparable, there being no significant difference; placebo 52 (3.0)%; nedocromil sodium 0.5 mg·ml^{-1}, 55 (4.0)%; 2.5 mg·ml^{-1}, 51 (5.0)%; and 10 mg·ml^{-1}, 52 (4.0)%. The maximal percentage falls post-treatment baseline FEV_1 in three exercise tests carried out at 15, 135 and 255 min after inhalation of placebo were also comparable and no significant difference was observed. The maximum percentage falls in FEV_1 (% predicted) after placebo and with nedocromil sodium 0.5, 2.5 and 10 mg·ml^{-1} concentrations are shown in table 1. The mean percentage protection effect of nedocromil sodium was significant at all three concentrations used compared to placebo in the first exercise test ($p<0.001$). There were no significant differences in the degree and the duration of protection in the second and third exercise tests. Although, the effect appeared to be waning with the lowest concentration (table 2).

Discussion

The patients in this study were selected on the basis that they had at least 40% protection with nedocromil sodium aerosol (4 mg), in order to allow us to demonstrate dose and duration effect. In a previous study, we observed that a small proportion of patients are not protected against exercise-induced asthma with sodium cromoglycate and nedocromil sodium [6, 8]. In this study, we had to exclude one patient for this reason. Nebulized nedocromil sodium administered 15 min before exercise challenge in concentrations from 0.5–10 mg·ml^{-1} was effective in attenuating the fall in

Table 1. – The pre-challenge mean (SEM) predicted FEV_1 (at 15 minutes post placebo and 3 doses of nedocromil sodium), and the maximum % falls in FEV_1 post exercise after placebo and 3 doses of nedocromil sodium in the 3 exercise tests performed at 15, 135 and 255 min after dosing.

	1st exercise				2nd exercise				3rd exercise			
	Placebo	0.5*	2.5*	10*	Placebo	0.5*	2.5*	10*	Placebo	0.5*	2.5*	10*
FEV_1 % pred pre-challenge	101 (9.6)	101 (9.6)	101 (9.6)	99 (9.9)	100 (9.5)	102 (9.4)	102 (9.5)	102 (9.5)	100 (9.5)	102 (9.6)	102 (9.5)	102 (9.5)
Maximum fall in FEV_1 % pred	70	89	92	91	66	84	91	90	64	83	87	82
FEV_1 % fall	31 (2.3)	12 (2.0)	9 (2.2)	8 (2.3)	34 (3.1)	18 (2.4)	11 (2.0)	12 (2.6)	36 (2.8)	19 (2.1)	15 (2.0)	20 (2.3)

*: nedocromil sodium dose in mg·ml^{-1}; FEV_1: forced expiratory volume in one second.

Table 2. – The maximal mean (SEM) percentage falls in FEV_1 post-exercise with placebo and percentage protection with nedocromil sodium in the three exercise tests performed at 15, 135 and 255 min after dosage

	Placebo Max. fall in FEV_1	Nedocromil sodium % protection 0.5*	2.5*	10*	p value
1st exercise	30.0 (2.1)	61.6 (8.7)	71.0 (4.3)	73.8 (5.6)	<0.001
2nd exercise	33.1 (3.1)	44.0 (11.2)	67.7 (6.2)	65.6 (7.1)	<0.001
3rd exercise	36.0 (2.9)	38.4 (9.0)	54.9 (9.0)	36.1 (9.5)	<0.001
p value		NS	NS	NS	

Mean relative humidity did not differ significantly on 4 study days. *: dose in mg·ml^{-1}; FEV_1: forced expiratory volume in one second; NS: nonsignificant.

FEV_1, with no significant difference in the inhibitory effect between the three concentrations. Repeat challenge up to 4 h after dosing demonstrated that the protective effect was still significant with no difference between doses. However, the effect, although still significantly different from placebo, was tending to diminish with time.

Thus, the response and duration of action of nedocromil sodium were not dose-dependent over the range of concentrations used. This contrasts with our earlier observations with sodium cromoglycate in exercise challenge where the protection with the lowest dose did not last beyond 2 h (2 mg) [7, 8]. The difference may reflect the fact that nedocromil sodium is more potent than sodium cromoglycate, as shown in some studies [9, 10], so that all the doses used in this study lie near the top of the dose-response curve. Use of lower concentrations 15 min before challenge would probably result in a dose-related and dose-duration response.

In a previous study [6], we observed that the dose-response of 0.5% (5 $mg \cdot ml^{-1}$) nebulized nedocromil and plasma concentration of the drug were similar to a 4 mg dose from the aerosol preparation already on the market. From this study, one might expect significant protection for at least 4 h against exercise-induced asthma from this aerosol preparation.

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