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Effects of nedocromil and salbutamol on airway reactivity in children with asthma

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Effects of nedocromil and salbutamol on airway reactivity in children with asthma. A. Pfleger, E. Eber, E. Weinhandl, M.S. Zach. ©ERS Journals Ltd 2002.

ABSTRACT: Nedocromil and salbutamol are effective drugs in preventing exercise-induced asthma (EIA). The aim of this study was to compare the protective effects of both drugs and a combination of both drugs against cold dry air-induced bronchoconstriction, using cold dry air challenges (CACh) as a surrogate for exercise.

Twenty-five atopic children (mean age 13.7, range 8–18 yrs) with EIA participated in the study. Lung function tests were performed before medication, 30 min after medication and just before CACh, and 3 and 15 min after the challenge on four consecutive days. CACh consisted of a 4-min isocapnic hyperpnoea of -10°C, absolutely dry air. Treatment consisted of nedocromil (two puffs of 2 mg) plus placebo, salbutamol (two puffs of 100 μg) plus placebo, the combination of both drugs, and placebo alone, in a random order.

Both active drugs were significantly more protective than placebo and the combination showed an additive effect. Mean maximum postchallenge decrease in forced expiratory volume in one second after placebo was 27±8.1%, 12±9.5% after nedocromil, 8±10.4% after salbutamol, and 4.5±6.7% after the combination of both drugs, respectively.

These results suggest that both drugs protect against exercise-induced asthma. Although not as effective as salbutamol and combined medication, nedocromil can give sufficient protection for many patients.

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Exercise-induced bronchoconstriction (EIB) is a common manifestation of bronchial asthma and is reported to occur in 40–90% of all paediatric patients [1, 2]. The most important mechanism responsible for triggering EIB is exercise-induced hyperpnoea [3–5]. Hyperpnoea effects respiratory water loss, mucosal drying and cooling [6, 7]. Recent work has suggested that the resulting hyperosmolarity of the epithelial lining fluid may lead to regulatory volume changes of airway epithelial cells [8, 9]. This results in the release of various bronchoconstrictive mediators from cells in the bronchial mucosa [10].

In susceptible patients, EIB is routinely prevented by inhaling a β_2-sympathomimetic bronchodilator before any physical exertion [11, 12]. Nedocromil sodium may reduce EIB by interfering with regulatory volume change in response to cell shrinkage [9]. It may therefore be an alternative to sympathomimetic bronchodilators for preventing EIB in susceptible asthma patients. However, there are substantial differences in the mode of action between these two premedications. While sympathomimetics predominantly prevent constriction of bronchial smooth muscle, nedocromil modifies the triggering event, thus reducing the release of mediators into the bronchial mucosa. As these mediators may not only have bronchoconstrictive but pro-inflammatory effects, the routine use of nedocromil as premedication for EIB might have some theoretical long-term advantages.

These long-term advantages, however, could only be of clinical relevance if the nedocromil-effected protection against EIB is of comparable magnitude to the one offered by sympathomimetic bronchodilators. Consequently, the current authors compared nedocromil with salbutamol, placebo, and a combined medication of nedocromil and salbutamol, respectively, to assess its relative protection against hyperpnoea-induced asthma in a double-blind, placebo-controlled study. A series of cold dry air hyperpnoea challenges was used as a surrogate for repeated exercise provocations [13–15].

Patients and methods

Subjects

Twenty-five paediatric and adolescent asthma patients (10 female, 15 male), with a mean age of 13.7 yrs (SD 2.57, range 7.8–17.8) and with exercise-induced asthma (EIA) participated in the study. Asthma was defined clinically according to the criteria of the American Thoracic Society [16]. On the basis of their history and a positive skin-prick test response to

one or several of 16 common allergens, they were all considered atopic. The patients' long-term anti-asthma treatment consisted of either inhaled budesonide (n=13), beclomethasone (n=1), fluticasone (n=3), nedocromil sodium (n=6) or sodium cromoglycate (n=2). Twenty-four hours prior to the study, this topical medication was stopped. In addition, no bronchodilator medication was taken for $\geqslant$12 h. None of the subjects had had a respiratory infection within the previous 6 weeks. Informed consent was obtained from both children and parents. The study was approved by the Ethics Committee of the Medical Faculty, University of Graz (Graz, Austria).

Design

This was a double-blind, placebo-controlled cross-over study. Each cold dry air challenge (CACh) was performed at 14:00 h. To compare the protective effect with cold dry air-induced bronchoconstriction, each patient was tested after each of the following four premedications, which were given in random order on 4 consecutive days. 1) Nedocromil verum (NV) (two puffs of 2 mg) and salbutamol verum (SV) (two puffs of 100 μg). Both drugs were inhaled by successive breaths through appropriate spacers (Fisonair®; Fisons Arzneimittel GmbH, Cologne, Germany, and Volumatic®; Glaxowellcome, Bad Oldesloe, Germany). 2) Nedocromil placebo (NP) (two puffs) and SV (two puffs of 100 μg), both administered as described above. 3) NV (two puffs of 2 mg) and salbutamol placebo (SP) (two puffs), both administered as described above. 4) NP (two puffs) and SP (two puffs), both administered as described above.

Methods

Pulmonary function tests (PFTs) were carried out on a pneumotachygraph spirometer (Pneumotest Junior; Jaeger, Würzburg, Germany), in accordance with standardised guidelines [17]. For each assessment, the patients performed forced vital capacity (FVC) manoeuvres, which were recorded in the form of maximum expiratory volume/time and flow/volume curves. FVC, forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), maximal expiratory flow at 50% (MEF_{50}) and at 25% (MEF_{25}) of remaining FVC were measured. These measurements were expressed in absolute terms and in per cent of predicted normal values, as based on established reference standards [18]. PFTs were carried out as baseline measurements 30 min after medication, *i.e.* just before CACh, and 3 and 15 min after CACh.

CACh was performed according to an established protocol [13, 14]. Cold dry air was produced by a commercially-available heat exchanger (RHES; Jaeger). Subjects hyperventilated absolutely dry, -10°C air at $FEV_1 \times 22.5$ for 4 min [13–15]. This level of hyperventilation was maintained by having the subjects compete with a target balloon. A carbon dioxide (CO_2)-analyser continuously monitored the CO_2 concentration in the expired air, and CO_2 was added to the inspired air in order to keep the subjects eucapnic.

CACh-induced lung function changes were expressed as percentage of baseline, as follows:

$$\Delta FEV_1(\%) = ((\text{pretest } FEV_1 - \text{post-test } FEV_1) / \text{pretest } FEV_1) \times 100 \quad (1)$$

Complete protection was considered to have been obtained when lung function changes 3 min after CACh remained within the range of normoreactivity, defined as $\Delta FEV_1 < -9\%$ [13].

If the FEV_1 15 min after CACh had not returned to $\geqslant$90% of the baseline value, the patient was treated with nebulised salbutamol. Such treatment was also administered when the patient felt any shortness of breath.

Statistical analysis

PFTs before and after the four premedications were compared by means of analysis of variance (ANOVA). The overall difference was tested with a repeated measurements model and *post hoc* multiple comparisons. The specific effect of the CACh response was defined as change in percentage from the post-medication value to the value 3 min after CACh. The specific effect was also tested with ANOVA and Waller-Duncan pairwise comparisons. A p-value of 0.05 was taken as the limit of statistical significance. For simplicity's sake, only the results for FEV_1 are reported. Findings for FVC, PEF, MEF_{50} and MEF_{25} are available on request.

Results

Individual baseline FEV_1 measurements and CACh-induced individual changes of FEV_1 after all forms of premedication are shown in table 1.

Baseline, postmedication (pre-CACh) and post-CACh (3 and 15 min) PFTs are summarised in table 2 and illustrated in figure 1. Baseline measurements did not differ between the four premedication regimens. Furthermore, there was no difference between the baseline values when analysed consecutively for the 4 study days. Both premedications containing salbutamol (NV+SV, NP+SV) effected statistically significant positive changes in FEV_1. CACh caused a statistically significant decrease (postmedication to 3 min post-CACh) of pulmonary functions for all four premedication regimens. All measurements had markedly improved 15 min post-CACh, but still differed significantly from the postmedication values.

Table 2 also contains a cross-sectional statistical comparison of measurements. All regimens containing salbutamol (NV+SV, NP+SV) produced significantly better postmedication measurements than those without (NV+SP, NP+SP). The best lung functions 3 min post-CACh were observed with the combination of both active drugs (NV+SV). Post-CACh values after all other premedication regimens were significantly lower. The CACh-induced fall of lung functions after

Table 1. – Baseline and cold dry air challenge (CACh)-induced changes in forced expiratory volume in one second (FEV_1)

Patient no.	Sex	Age yrs	FEV_1	ΔFEV_1 % preCACh			
			Baseline	Placebo	Salb.	Ned.	Salb./Ned.
1	M	17.8	4.44	-33.9	-6.3	-13.9	-9.3
2	F	9.9	1.98	-56.3	-27.1	-0.6	-2.2
3	M	16.9	3.96	-59.4	-15.1	-15.5	-6.5
4	M	17.4	3.84	-36.3	-15.3	-21.9	-9.5
5	M	14.2	2.89	-49.0	-6.3	-37.5	-30.8
6	F	15.5	2.78	-1.1	-0.9	-1.1	-8.4
7	F	14.3	2.91	-15.8	-1.6	-10.9	-0.7
8	M	10.6	2.16	-12.4	-1.0	-6.8	0.4
9	M	14.0	3.27	-8.8	-2.0	-8.5	1.8
10	F	12.9	2.27	-69.9	-17.1	-11.8	-11.2
11	F	14.5	1.91	-43.5	-46.6	-24.1	-5.9
12	F	10.0	1.55	-26.3	-7.2	-17.7	-6.0
13	M	14.6	3.6	-23.9	-2.2	-13.0	-1.2
14	M	12.8	1.88	-10.5	-2.6	-7.1	0.9
15	M	10.7	2.07	-12.1	-7.4	-6.3	-1.0
16	M	12.0	2.46	-8.4	-2.1	-8.7	0.7
17	M	12.4	2.51	-5.6	-3.7	-0.5	1.2
18	F	7.8	1.40	-7.2	0.1	-3.5	-0.8
19	M	12.9	2.47	-24.9	-2.0	-6.0	0.6
20	F	14.8	3.14	-33.3	-0.3	-8.4	-2.6
21	M	17.5	3.38	-34.8	-4.6	-6.0	-1.5
22	F	14.7	2.67	-35.0	-15.4	-27.3	-5.9
23	F	14.0	3.42	-25.6	-3.8	-2.5	-2.7
24	M	16.3	4.43	-31.6	-8.3	-25.5	-4.5
25	M	15.1	4.08	-32.6	-9.6	-18.8	-7.0
Mean		13.7	2.9	-27.9	-8.3	-12.2	-4.5
SD		2.6	0.9	18.1	10.4	9.5	6.7

M: male; F: female; Salb.: salbutamol; Ned.: nedocromil.

nedocromil premedication (NV+SP) was comparable to that after salbutamol (NP+SV). However, as the latter started from a bronchodilator-induced higher postmedication (pre-CACh) level, the post-CACh values after nedocromil (NV+SP) and salbutamol (NP+SV) remained significantly different. Post-CACh measurements after the placebo combination (NP+SP) were significantly lower than those after any of the other premedications. All values improved again from the 3 to the 15 min post-CACh assessment, but most cross-sectional differences between the four different premedication regimens remained statistically significant.

The CACh-induced lung function changes are listed and statistically compared in table 3 and illustrated in figure 2. The biggest 3-min post-CACh change was observed after the placebo combination (NP+SP) and this change differed significantly from all the changes that were observed for the other premedication regimens. Changes from postmedication (pre-CACh)

Table 2. – Baseline, postmedication (pre-CACh), and post-CACh forced expiratory volume in one second (FEV_1) measurements

	FEV_1			
	Baseline	Postmedication	3 min post-CACh	15 min post-CACh
Placebo	97.63±11.56	97.50±11.55	69.79±17.34¶	78.26±16.40¶
Ned.	96.14±11.12	97.98±11.96	86.23±14.14¶	93.94±11.35¶
Salb.	96.96±12.37	104.77±11.02#	95.90±13.83¶	100.48±11.30¶
Ned./Salb.	96.95±11.85	105.86±11.02#	101.07±12.31¶	102.62±12.93¶
Placebo *versus* Ned.	NS	NS	<0.001	<0.001
Placebo *versus* Salb.	NS	<0.001	<0.001	<0.001
Placebo *versus* Ned./Salb.	NS	<0.001	<0.001	<0.001
Ned. *versus* Salb.	NS	<0.001	<0.001	<0.001
Ned. *versus* Ned./Salb.	NS	<0.001	<0.001	<0.001
Salb. *versus* Ned./Salb.	NS	NS	<0.05	NS

Data are presented as % pred mean±SD or as p-values. CACh: cold dry air challenge; Ned.: nedocromil; Salb.: salbutamol; NS: nonsignificant. #: statistically significant difference from baseline to postmedication value; ¶: statistically significant difference from postmedication preCACh to postCACh value.

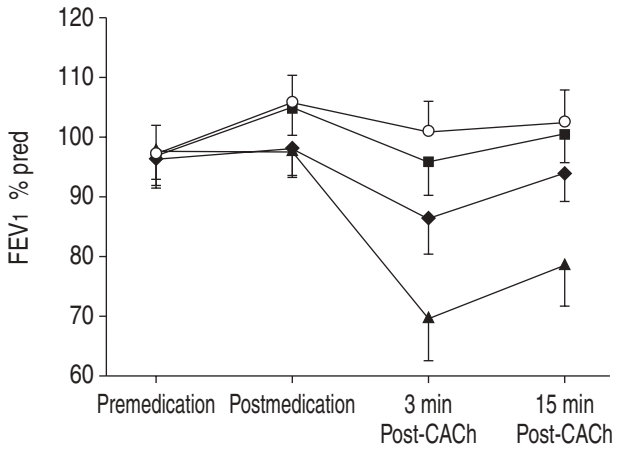

Fig. 1. – Baseline, postmedication (pre-cold dry air challenge (CACh)) and postchallenge values of forced expiratory volume in one second (FEV_1) of all four premedications (▲: placebo; ◆: nedocromil; ■: salbutamol; ○: salbutamol and nedocromil). Data are presented as % pred mean±95% confidence intervals.

values to those measured 15 min post-CACh were smaller, but the difference between the placebo combination (NP+SP) and all other premedications was retained. The smallest CACh-induced lung function change was observed after the combination of active drugs (NV+SV). This change differed significantly from that of the nedocromil premedication (NV+SP) measurements. When compared to the salbutamol premedication (NP+SV) changes, however, there was no significant difference for FEV_1. Postmedication to 15 min post-CACh changes did not differ between any of the active medication regimens.

When defining protection against CACh-induced lung function changes as a fall of FEV_1 that remained within the limits of normoreactivity, 21 of 25 patients (84%) were protected with the combination of both active drugs (NV+SV), 18 (72%) with salbutamol (NP+SV), 13 (52%) with nedocromil (NV+SP), and five (20%) with the placebo combination (NP+SP), respectively. The maximum individual CACh-induced

Table 3. – Postchallenge fall of forced expiratory volume in one second (FEV_1) (% pre-CACh)

	FEV_1	
	3 min post-CACh	15 min post-CACh
Placebo	27.93±18.10	19.30±17.17
Ned.	12.15±9.46	4.12±4.80
Salb.	8.33±10.36	3.99±5.91
Ned./Salb.	4.49±6.67	3.14±6.09
Placebo *versus* Ned.	<0.001	<0.001
Placebo *versus* Salb.	<0.001	<0.001
Placebo *versus* Ned./Salb.	<0.001	<0.001
Ned. *versus* Salb.	NS	NS
Ned. *versus* Ned./Salb.	<0.001	NS
Salb. *versus* Ned./Salb.	NS	NS

Data are presented as mean±SD or as p-values. CACh: cold dry air challenge; Ned.: nedocromil; Salb.: salbutamol; NS: nonsignificant.

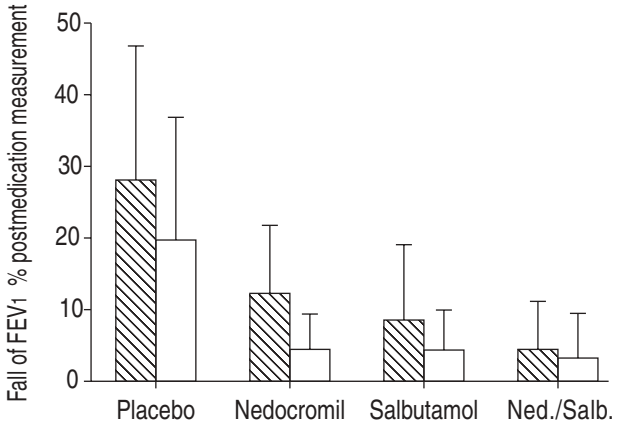

Fig. 2. – Per cent fall in forced expiratory volume in one second (FEV_1) after 3 min (▨) and 15 min (□) after cold dry air challenge and different premedications. Data are presented as mean±SD. Ned.: nedocromil; Salb.: salbutamol.

fall of FEV_1 was observed under the placebo combination (NP+SP) in 22 children, under nedocromil premedication (NV+SP) in one, under salbutamol premedication (NP+SV) in one, and under the combination of both active drugs (NV+SV) in one child, respectively.

Discussion

The present study shows that nedocromil offers significant protection against a CACh. However, this protection, both in terms of the mean protection and the number of patients with a normalised response, was somewhat less than the one achieved by salbutamol premedication. Maximum protection was observed with the combination of both active drugs, in keeping with a different mode of action.

This is the first study to directly compare the protective effects of nedocromil and a β_2-sympathomimetic premedication against isocapnic hyperpnoea-induced bronchoconstriction in children with bronchial asthma. This protective effect of nedocromil has previously been documented in several placebo-controlled paediatric [19–24] and adult studies [25–30]. One previous paediatric investigation compared salbutamol to a combination of nedocromil and salbutamol and found that both regimens offered substantial protection [31]. More recently, nedocromil was shown to protect against the consequences of epithelial lining fluid hyperosmolarity, by interfering with regulatory cell volume changes [9]. As indicated by bronchoalveolar lavage findings, such cell volume changes lead to EIB *via* release of various mediators from different cell systems [10]. Whether these mediators are only responsible for bronchoconstriction or also have some pro-inflammatory effects, remains unclear. However, late asthmatic reactions after strenuous physical exercise [30, 32] and the recent observation of an increased asthma prevalence in competitive track and field athletes as well as swimmers [33, 34], suggest that repeated exercise-induced hyperpnoea might have the potential to induce the

manifestation or exacerbation of bronchial asthma. Speculatively, this might be understood as the long-term consequence of the above-mentioned mediator release.

If this was a valid hypothesis, any premedication with sympathomimetic bronchodilators could be seen as a management strategy with limited therapeutic long-term value. By interfering with the constriction of bronchial smooth muscle, bronchodilators will predominantly ameliorate the last step of the reaction cascade that leads to EIB, while having only a little effect on the preceding release of mediators. From a long-term perspective, this might be disadvantageous, as it could allow for ongoing perpetuation of the bronchial inflammation while preventing any perceivable warning by immediate bronchoconstriction. This concern finds some support in the observation of more severe EIB with the chronic daily use of sympathomimetic bronchodilators [35]. In addition, it has been speculated that such chronic use of β_2-adrenoceptor agonists, which stimulates the secretion of chloride ions, might cause an accelerated loss of cell volume, thus facilitating the trigger mechanism for EIB [8, 9].

As shown by the present study, nedocromil significantly reduces both the occurrence and the severity of EIB. In fact, it affected approximately two thirds of the protection that was observed after premedication with a β_2-sympathomimetic bronchodilator. As nedocromil is thought to interfere with the development of EIB by reducing initially occurring cell volume changes [9], it should also ameliorate the consecutive mediator release into the respiratory mucosa. However, this second therapeutic effect, which should be beneficial in the long term, remains speculative at present, as it is based on theoretical reasoning only and is not yet supported by relevant study results. Thus, it would be interesting to follow up the present findings with a bronchoalveolar lavage project, comparing dry air hyperpnoea-induced mediator release after nedocromil and placebo premedication. For obvious ethical reasons, such an investigation should not be performed in paediatric patients but rather in adult volunteers with bronchial asthma.

The findings of the present study, in combination with the above theoretical considerations, might have some practical implications for the clinical management of EIB in susceptible asthma patients. In the long term, patients who are sufficiently protected by nedocromil might benefit from using nedocromil rather than sympathomimetic bronchodilators for premedication against EIB. The other subgroup, *i.e.* patients who still require a β_2-adrenoceptor agonist for sufficient amelioration of EIB, could also receive some long-term benefit from combining the β_2-adrenoceptor agonist with nedocromil. Clearly, as these speculations are based on the present study results, they only pertain to the premedication routine for prevention of EIB. Any such premedication, however, should be seen as an adjunct and not as a substitute for the basic routine of an anti-inflammatory long-term medication.

One interesting side product of this study is the finding of a high prevalence of airway hyperresponsiveness in a group of paediatric asthma patients that were considered to be well stabilised by long-term medication, as judged by routine clinical and lung function criteria. Others have made similar observations and have shown that monitoring of anti-asthma management by additional measurements of non-specific bronchial responsiveness can lead to a significantly better long-term outcome in terms of exacerbation frequency, lung function and bronchial histology [36]. This raises the question as to whether the assessment of bronchial responsiveness, as a surrogate marker of bronchial inflammation, should be included in the routine monitoring of asthma patients.

The present study used a CACh, *i.e.* the voluntary hyperpnoea of cold and absolutely dry air, as a laboratory model for EIB. Earlier work has shown that exercise-induced hyperpnoea is responsible for triggering EIB [3–5]. CACh is meanwhile a well-standardised bronchial provocation technique that has been used mainly as a paediatric research tool [13–15]. As the trigger mechanism can be dimensioned with considerable accuracy in CACh, the use of this technique had the advantage of highly-reproducible stimulus for the series of four challenges which had to be performed in the present study.

In conclusion, this study showed that nedocromil offers substantial protection against hyperpnoea-induced bronchoconstriction, both in terms of reducing the dimension of the reaction and of normalising bronchial responsiveness in some asthma patients. However, the protection offered by salbutamol premedication remained superior to that after nedocromil. Maximum protection was most often achieved with the combination of both substances. As nedocromil interferes with the first step of the reaction cascade that leads to exercise- or hyperpnoea-induced bronchoconstriction, it might have long-term advantages over salbutamol by more potently reducing the pro-inflammatory mediator load on the bronchial mucosa. Whether this calls for a change in the premedication routine against exercise-induced bronchoconstriction or not, should be subject to further investigation.

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