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The combined effect of nifedipine and sodium cromoglycate on the airway response to inhaled hypertonic saline in patients with bronchial asthma

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ABSTRACT: The combined effect of oral nifedipine and aerosolized sodium cromoglycate on the airway response to inhaled sodium chloride at increasing concentrations was randomly studied in 10 patients with bronchial asthma. Nifedipine (20 mg) protected the airways in 6 of the 10 patients, and sodium cromoglycate (20 mg) in all the 10 patients. Following both drugs, the airway response to hypertonic saline was further reduced when compared to each drug on its own. It is concluded that the combination of nifedipine with sodium cromoglycate might be of benefit in the treatment of difficult asthmatic patients.

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The inhalation of ultrasonically nebulized solutions of either low or high osmolality triggers bronchial obstruction in patients with bronchial asthma [1–4]. Mast cells release mediators following these stimuli [5, 6], thereby inducing bronchial obstruction by either direct smooth muscle effect or *via* stimulation of irritant receptors.

Calcium transport is essential for smooth muscle contraction and for secretory processes [7]. Indeed, calcium blockers such as nifedipine and verapamil prevented bronchial obstruction induced by various stimuli such as exercise [8], cold air [9] antigen provocation [10] as well as histamine and methacholine [11, 12]. In a clinical trial [13], nifedipine was of no benefit in patients with bronchial asthma. Since higher doses of either nifedipine or verapamil cause side effects, combining these drugs with other anti-asthmatic drugs might prove to be beneficial in treating patients with asthma.

Sodium cromoglycate (SCG), a widely used drug in the prevention of bronchial asthma [14], prevented Ca^{++} transport through basophils [15]. Assuming that nifedipine and SCG prevent Ca^{++} transport at different sites, we studied the combined effect of these two drugs on bronchial obstruction induced by inhalation of hypertonic saline.

Patients and methods

Ten asthmatic patients (3M and 7F) participated in the study. Their ages ranged from 16–48 years with a mean±SD: 24±9 yrs. All patients met the following diagnostic criteria:

1. Clinical bronchial asthma, as defined by the American Thoracic Society with laboratory proof for exercise-induced asthma;
2. No patient had cardiovascular disease or chronic obstructive lung disease other than bronchial asthma;
3. A reduction of at least 15% in FEV_1 (forced expiratory volume in one second) after inhalation of increasing concentrations of hypertonic saline;
4. None of the patients had viral respiratory infections in the preceding 6 weeks.

All the patients completed the study in no longer than 2 weeks. All patients were symptom-free during the experiments and were able to stop bronchodilating therapy for at least 24 hrs.

The study was approved by the hospital's Helsinki Committee and all the patients signed an informed consent. Also, the parents of patients 4 and 9 signed consent forms.

Spirometry, with an Ohio 842 spirometer, was done at rest and for the determination of bronchoconstrictive response to various stimuli. The best of three tests was chosen.

Inhalation challenge

Each patient inhaled for 5 min from each of the following NaCl concentrations: 0.9%, 2.5%, 5%, 10% and 20% given by ultrasonic nebulizer (De Vilbiss). Five

minutes after each inhalation repeated spirometry was done. The challenge was stopped when a 15% reduction in FEV_1 was achieved or the highest concentration of hypertonic saline was attained. At the end of each bronchial challenge, salbutamol was inhaled.

The protocol consisted of performing the above-mentioned bronchial provocation 30 minutes after each of the following therapies, at the same time on separate days in a single blind manner.

1. Placebo: inhalation of 2 ml of normal saline together with placebo capsule.
2. Inhalation of 2 ml solution containing 20 mg sodium cromoglycate, plus placebo capsule.
3. 20 mg nifedipine given orally by capsule, together with placebo aerosol.
4. Oral capsule of 20 mg nifedipine together with inhalation of 20 mg sodium cromoglycate. The treatments were given in random order.

pulse. There was no significant difference between the baseline FEV_1 of the four study days.

There was no significant effect of either nifedipine or sodium cromoglycate on baseline FEV_1 at 30 min post administration. The inhalation of NaCl following both placebos induced a significant drop in FEV_1 in all the patients with a mean PC_{15} of 3.3% (±0.8%) sodium chloride, and a range of 2.1–4.4%.

Table 2 shows the effect of placebo, nifedipine and SCG on PC_{15}. In comparison with placebo, SCG significantly increased the PC_{15} in all the 10 patients studied ($p<0.01$). The mean PC_{15} was 6.8±1.5%. With 20 mg nifedipine, 6 of the 10 patients raised their PC_{15}. The mean PC_{15} for the group was 7.5±5%. This change was statistically significant when compared to placebo ($p<0.05$).

The administration of both drugs 30 min before the provocation further increased the PC_{15} to hypertonic

Table 1. – Patient characteristics

No.	Sex	Age	Baseline FEV_1		ΔFEV_1 after provocation*		ΔFEV_1 after salbutamol**	
			$l \cdot s^{-1}$	% pred	$l \cdot s^{-1}$	% pred	$l \cdot s^{-1}$	% pred
1	M	19	3.0	61	0.7	-22	0.8	+33
2	F	19	2.5	63	0.6	-24	0.7	+37
3	F	36	1.6	57	0.3	-17	0.3	+26
4	M	15	3.0	83	0.5	-17	0.6	+24
5	M	24	3.4	59	1.2	-35	1.3	+61
6	F	24	1.9	73	0.7	-34	0.9	+76
7	F	22	2.5	84	0.6	-24	0.5	+25
8	F	48	1.7	77	0.3	-17	0.2	+15
9	F	14	2.0	69	0.4	-21	0.9	+60
10	F	18	3.0	85	0.8	-27	1.2	+57
Mean		24	2.5	71	0.6	24	0.8	41
±SD		9	0.6	10	0.1	6.2	0.3	19

FEV_1 values from the placebo day. * Δ% FEV_1 after provocation - percent change from baseline;
** Δ % FEV_1 after salbutamol - percent change from post saline value.

Analysis of data

The provocation concentration of NaCl, including 15% fall in FEV_1 (PC_{15}) was calculated from the semilogarithmic dose response curve, obtained from plotting the change in FEV_1 against the increasing concentration of NaCl.

The data were analyzed by the one-way analysis of variance, with statistical significance defined as $p<0.05$.

Results

The anthropometric data of the studied patients are summarized in table 1. The mean baseline FEV_1 for the whole group, taken from the placebo day, indicates a mild degree of airway obstruction (mean±SD) of 71±10%. In all the patients, hypertonic saline induced a significant drop in FEV_1 which was reversible by inhaled salbutamol. Following nifedipine two patients had facial flushing with no effect on blood pressure or

Table 2. – The effect of nifedipine and sodium cromoglycate on airway response to hypertonic saline (PC_{15}, % NaCl) expressed as the % sodium chloride giving a 15% fall of FEV_1

No	Placebo	Nif 20 mg	SCG	SCG + Nif 20 mg
		% Sodium chloride		
1	3.4	16.7	5.8	>20
2	3.1	2.3	5.8	>20
3	4.4	9.3	9.4	>20
4	4.4	4.7	6.8	>17
5	2.1	5.0	4.8	9.5
6	2.2	5.7	5.4	11
7	3.1	2.3	5.0	11
8	4.4	17.6	8.3	>20
9	3.6	3.6	6.0	11
10	2.8	8.3	8.3	>20
Mean	3.3	7.5	6.8	
±SD	0.9	5.2	1.5	
±SE	0.3	1.7	0.5	

Nif - Nifedipine; SCG - sodium cromoglycate

saline. This effect was seen in all the patients. In 5 of them, no bronchoconstriction could be seen even when 20% NaCl was inhaled. The effect of both drugs combined was superior to either drug given separately prior to provocation.

One way analysis of variance done for placebo, nifedipine and SCG, showed significant change in PC_{15}. In an attempt to compare the effect of the combined therapy, Group 4 was included in the ANOVA, giving all the PC_{15} who were >20% a value of 20% NaCl. Group 4 was far superior to any of the other treatments.

The mean of the four samples were significantly different with $p<0.0001$. Similar results were obtained when V_{max50}%VC was analyzed.

In fig. 1, individual dose response curves for all study days are shown.

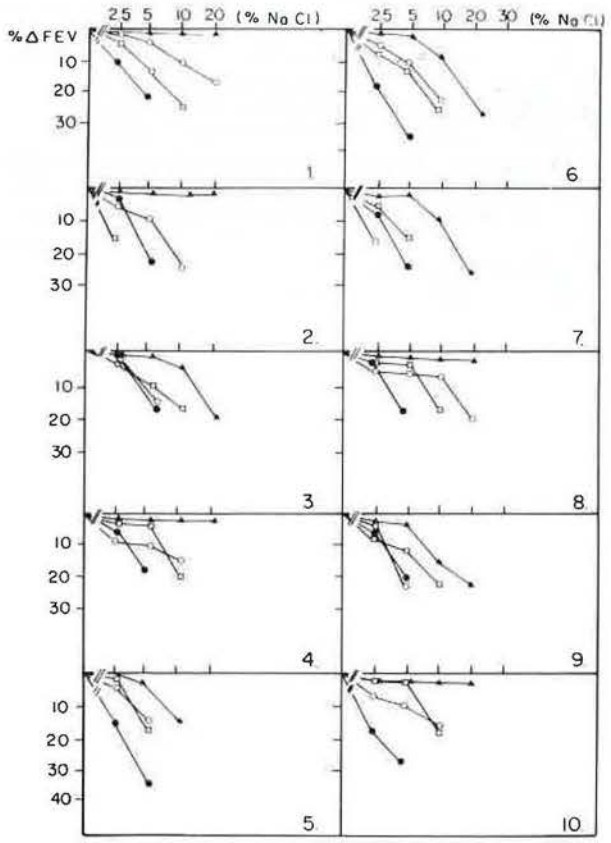

Fig. 1. – Individual dose response curve for all study days between FEV_1 ($l \cdot s^{-1}$) and % NaCl following placebo (●), SCG (□), Nif (○) and SCG + Nif (▲).

Discussion

In vitro studies showed that calcium blockers prevented bronchial smooth muscle contraction, as well as mast cell degranulation [7].

In human experiments calcium blockers (verapamil and nifedipine) were effective in preventing bronchial obstruction induced by exercise, cold air and antigen provocation [8–10]. Similar protection was also demonstrated following pre-treatment with SCG, a drug recently shown to have calcium blocking properties. Since different calcium blockers might have different sites of action, one might assume that the combined effect of these blockers on airway hyperreactivity will be augmented. Therefore, the effect of these drugs separately and in combination, was investigated in our study.

As a non-specific airway stimulus, we chose increasing concentrations of ultrasonically nebulized NaCl. Hypertonic NaCl induced reproducible bronchial obstruction in a dose dependent fashion [3], and is a sensitive test in detecting airway hyperreactivity in patients with bronchial asthma. From the dose-response curves, the provocation concentration inducing a 15% drop in FEV_1, was calculated. When SCG was given, there was a significant shift in the dose response curve in all the subjects of the study group. Similar results were published by SHOEFFEL *et al.* [2] who demonstrated that SCG prevented the airway response to inhaled 3.6% NaCl.

In our study, 20 mg nifedipine was clearly effective in preventing bronchial obstruction in six of the studied patients. A support for these results came from the study of CERRINA *et al.* [8], who successfully prevented exercise-induced asthma by pre-treatment with 20 mg nifedipine. However, in the study of SHOEFFEL *et al.* [2], verapamil did not prevent the bronchoconstrictor response to 3.6% NaCl. The combination of 20 mg nifedipine and inhaled 20 mg SCG was superior to either drug on its own. This effect was also seen in the four patients who had no protection from 20 mg nifedipine given alone. Five of the patients had no bronchial obstruction even at the largest concentration of inhaled NaCl.

Nifedipine at a dose of 20 mg given orally was reported to prevent bronchial obstruction to various stimuli [8, 9], but showed no therapeutic benefit when given to patients with bronchial asthma. Higher doses cause serious side effects. In order to avoid increasing side effects we added SCG, which probably effects Ca^{++} transport at a different site.

Combining Ca^{++} blockers with other anti-asthmatic drugs has been tried previously. LEVER *et al* [16] demonstrated enhancement of bronchodilating effect of salbutamol when nifedipine was added. The effect of nifedipine was strongest four hours after the administration of salbutamol. In our study, the effect of Nifedipine on the airways was measured only 30 min after its administration.

This study clearly supports the concept of adding calcium blockers to anti-asthmatic drugs to modifying airway hyperreactivity.

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Effet combiné de la nifedipine et du cromoglycate disodoqie sur la réponse des voies aériennes à une solution saline hypertonique en inhalation chez des patients atteints d'asthme bronchique. S. Kivity, R. Ganem, J. Greif, M. Topilsky

RÉSUMÉ: Nous avons étudié de manière randomisée, chez 10 patients asthmatiques, l'effet combiné de la nifedipine par voie orale et d'aérosols de cromoglycate disodique sur la réponse des voies aériennes à des solutions de chlorure à concentrations croissantes. La nifedipine (20 mg) a protégé les voies aériennes chez 6 des 10 patients, et le cromoglycate disodique (20 mg) chez les 10 patients. Si l'on administre les deux drogues, la réponse des voies aériennes à la solution saline hypertonique est réduite davantage par rapport à celle obtenue après chacune des drouges séparément. L'on conclut que la combinaison de la nifedipine au cromoglycate disodique pourrait être utile dans le traitement de certains asthmes difficiles à contrôler.

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