

Clinical aspects of allergic disease

Inhibition of the late asthmatic response by nedocromil sodium administered more than two hours after allergen challenge

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Fourteen adult patients with bronchial asthma who were known late responders to bronchial allergen challenge were entered into a double-blind crossover study to compare the protective effects of nedocromil sodium (3×4 mg) and placebo aerosols on the late asthmatic response (LAR). After screening for development of an LAR (fall in forced expiratory volume in 1 second [FEV₁] $\geq 20\%$ at at least 3 consecutive time points, 4 to 10 hours after challenge), patients were randomized to test treatment on 2 study days, with an interval of at least 3 days. Nine of the patients had a dual late response, which is a combination of an immediate and a late response, and five other patients had an isolated late response only. On each study day the concentration of allergen that previously elicited a response was inhaled for 10 minutes. FEV₁ was recorded every 10 or 15 minutes for up to 1 hour after challenge, and then at hourly intervals for 12 hours and every second hour on the next 2 days. Test treatments were administered in three doses at 30-minute intervals, with the first dose given 90 minutes before the expected onset of the LAR for each patient. Compared with placebo, nedocromil sodium significantly inhibited the LAR ($p < 0.05$) at each time point measured from 6 to 10 hours after challenge and reduced the maximum fall in FEV₁ by 21.0% overall ($p = 0.003$). (J ALLERGY CLIN IMMUNOL 1993;92:19-28.)

Key words: Late asthmatic response, effects of nedocromil sodium

Patients with bronchial allergy, having been challenged by allergen, may develop different types of asthmatic (bronchus-obstructive) response.¹⁻⁸ The immediate asthmatic response (IAR) has been repeatedly described.^{1, 4}

Other, so-called "nonimmediate asthmatic responses," the late asthmatic response (LAR) being one of them, were also described in our previous articles.^{5-7, 9-13} The LAR is a well recognized clinical phenomenon in patients with bronchial asthma.^{1-3, 5-7, 10-15}

Abbreviations used

BPT:	Bronchial provocation test
BDP:	Beclomethasone dipropionate
DSCG:	Disodium cromoglycate
FEV ₁ :	Forced expiratory volume in 1 second
IAR:	Immediate asthmatic response
LAR:	Late asthmatic response
NS:	Nedocromil sodium
PBS:	Phosphate-buffered saline
VC:	Vital capacity

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Its incidence has been variously quoted as about 50% in adults² and up to 73% in some selected groups of children,³ after allergen challenge. The LAR may occur in two clinical forms, as an isolated form or as a part of a dual response, in which an early response precedes the late one.^{6, 11}

In our previous studies, which included large groups of patients with bronchial asthma ($n = 251$), 24% of the patients developed an LAR to allergen challenge, 10% demonstrated an

TABLE I. Patient characteristics

Patient No.	Age (yr)	Sex	Histamine PD ₂₀ (mg/ml)	Bronchial challenge		Nonpretreated response [FEV ₁]					Treatment order
				Allergen	Dose/ml	Baseline (L)	IAR	LAR			
							Max.fall (%)	Onset (hr)	Max.fall (%)		
Dual response											
2	46	M	16	HD	5.0 mg	4.7	31	6	34	b	
4	20	F	8	HD	0.5 mg	2.5	32	5	36	b	
5	42	M	> 32	GP	10,000 NU	3.9	25	4	26	a	
6	28	M	32	GP	1000 NU	5.3	43	6	40	a	
7	22	F	8	HD	1.0 mg	2.7	26	7	44	a	
8	19	M	> 32	GP	1000 NU	3.6	34	5	39	a	
9	27	F	> 32	HD	0.5 mg	3.3	33	7	39	a	
10	26	F	16	GP	10,000 NU	1.6	38	6	38	b	
13	25	F	32	HD	1.0 mg	3.4	42	5	38	b	
Isolated LAR											
1	25	F	> 32	GP	10,000 NU	3.0	—	6	37	b	
3	25	F	16	GP	10,000 NU	2.1	—	5	38	a	
11	32	F	> 32	HD	0.5 mg	3.0	—	6	50	b	
12	28	M	32	HD	5.0 mg	4.4	—	5	30	b	
14	25	F	> 32	HD	1.0 mg	3.6	—	4	44	a	

Treatment order: a = nedocromil sodium/placebo; b = placebo/nedocromil sodium.

PD₂₀, Provocative dose causing a 20% fall in FEV₁; HD, house dust; GP, grass pollen; NU, Noon units.

isolated form of LAR, and 14% showed a dual form of LAR.⁶ The exact pathophysiologic and immunologic mechanisms presumably underlying the LAR and its different subforms have not yet been satisfactorily clarified.¹² However, in contrast to the IAR, there is strong evidence for involvement of various inflammatory mechanisms in the LAR.^{6, 7, 12-14, 16}

Nedocromil sodium (NS), the disodium salt of a novel pyranoquinoline dicarboxylic acid, demonstrated antiallergic and antiinflammatory effects both in animal and human studies, especially in the respiratory tract.¹⁷⁻²²

The protective effects of NS on the LAR in patients with bronchial asthma have already been reported.^{22, 23} However, only the LAR, being a part of dual response, has been studied, and NS was administered before the allergen challenge.²²

Few data are available to illustrate the possible protective effects of NS on the isolated form of LAR. There is also a dearth of information concerning the effects of NS administered in a single dose after the allergen challenge, before the predicted onset of the LAR.

The purpose of this study was to investigate: (1) the effects of NS as a single prophylaxis if administered after the allergen challenge, just before

the predicted onset of LAR; (2) the existence of some differences in the effects of NS on the isolated form of LAR and that being a part of the dual response; (3) the indication for the use of NS in cases of LAR.

METHODS

Patients

Fourteen patients who had allergic bronchial asthma that required regular therapy (13 inhaled bronchodilators, 5 inhaled corticosteroids and 6 inhaled cromolyn) and who developed an LAR to bronchial provocation test (BPT) with an inhalant allergen were randomly selected for this study. The patients ranged in age from 19 to 46 years (Table I). They all showed reversible bronchoconstriction alternating with symptom-free periods. Their pulmonary function did not demonstrate any restrictive changes, and they did not have chronic infections of the airways; none had received immunotherapy or orally administered corticosteroids in the past. None of the female participants were pregnant. All patients were previously examined by the following diagnostic procedure: (1) a general part including disease history, physical examination, basic laboratory tests, chest x-ray, electrocardiogram, pulmonary functions and blood gases; (2) an allergologic and immunologic part including skin tests, bronchial histamine threshold (provocative dose causing a 20% decrease in forced expiratory volume in 1 second [FEV₁]), blood leukocyte and eosinophil count, total serum IgE (paper

TABLE II. Bronchial and general complaints accompanying the nonpretreated and pretreated late asthmatic response (LAR)

	LAR		
	Nonpretreated	NS	Pretreated with Placebo
Dyspnea	+++	±	+++
Wheezing	+	—	+
Cough	+	—	+
Expectoration—thick sputum	+	—	++
Pressure on the chest	++	—	+
Chills	+	—	+
Tiredness	+	—	+
Headache	++	+	++
Weakness	+++	+	+++
General malaise	++	—	++
Increase in body temperature*	+	—	+

The appearance of the symptoms: —, No appearance; +, slight degree; ++, moderate degree; +++, distinct degree.

*Higher than 37° C = 98.6° F axillary.

radioimmunosorbent test), specific serum IgE (RAST), total serum IgG, IgM, and IgA (single radial immunodiffusion), and bronchial challenges with inhalant allergens, recorded up to 56 hours.

All bronchial challenges were performed during hospitalization of the patients under standard conditions.^{4, 6} At the start of the study all patients were free of symptoms of asthma and infections and had a baseline FEV₁ of 80% or more of predicted value. Anti-allergic therapy (cromolyn, inhaled corticosteroids, long-term-acting oral antihistamines) had been withdrawn for at least 6 weeks, short-term-acting antihistamines for at least 12 hours, and inhaled short-term-acting bronchodilators (β_2 -agonists) for at least 8 hours before the study. In cases in which FEV₁ or both FEV₁ and vital capacity (VC) decreased by 50% or more during the BPTs, a single inhalation of 100 μ g of salbutamol aerosol was given to prevent a further decrease in FEV₁. If more extensive treatment was necessary, the patient was excluded from the study. The study was approved by the Hospital Ethical Committee, and informed consent was obtained from each participant.

Allergens

The dialyzed and lyophilized extracts (Allergen Laboratory Diephuis, Groningen, The Netherlands) were diluted in phosphate-buffered saline (PBS). The basic (undiluted) concentrations of allergens used for bronchial challenges were as follows: house dust, 5 mg/ml; and grass pollen, 10,000 NU/ml. The allergen extracts used for skin tests were diluted 10 times.

BPTs

The VC and FEV₁ were recorded by means of a spiograph (model D-75, LODE, The Netherlands).

FEV₁ was considered to be the basic parameter for assessment of the bronchial obstruction. Both PBS and allergen extracts were inhaled in the form of an aerosol administered by means of the Wiesbadener Doppel-Inhalator at an air flow of 10 L/min. The aerosol particles had a mass median diameter of 2.8 to 3.6 μ m.

The bronchial challenge was performed according to the following schedule:^{4, 6, 9} (1) recording of the base values ("initial values") at 0, 5, and 10 minutes; (2) inhalation of PBS for 10 minutes followed by recording of the "PBS values" (control) at 0, 5, and 10 minutes; (3) inhalation of the allergen aerosol for 10 minutes (2 $\times$ 5 minutes) followed by recording of the VC and FEV₁ values at 0, 5, 10, 20, 30, 45, 60, 90, and 120 minutes and then every hour up to the twelfth hour and every second hour between the twenty-fourth and thirty-eighth hours and between the forty-seventh and fifty-sixth hours after the challenge. The BPTs were evaluated as follows: (1) the decrease of FEV₁ or both FEV₁ and VC of less than 10% with respect to the control values as negative, from 10% to 20% as doubtful, and of 20% (provocative dose causing a 20% fall in FEV₁) or more as positive; (2) the decrease in FEV₁ within 60 minutes after allergen challenge, recorded at a minimum of three consecutive time intervals, was considered to be a positive IAR; the decrease in FEV₁ within a period of 4 to 24 hours after allergen challenge, recorded at a minimum of three consecutive time intervals was considered to be a positive LAR. All bronchial challenges were performed with allergen extracts in a standard dilution sequence (pollen allergens 1:100, 1:10, and undiluted; and perennial allergens 1:10, 1:5, 1:2, and undiluted), with respect to the basic concentrations described above. A time interval of 6 days was always inserted between

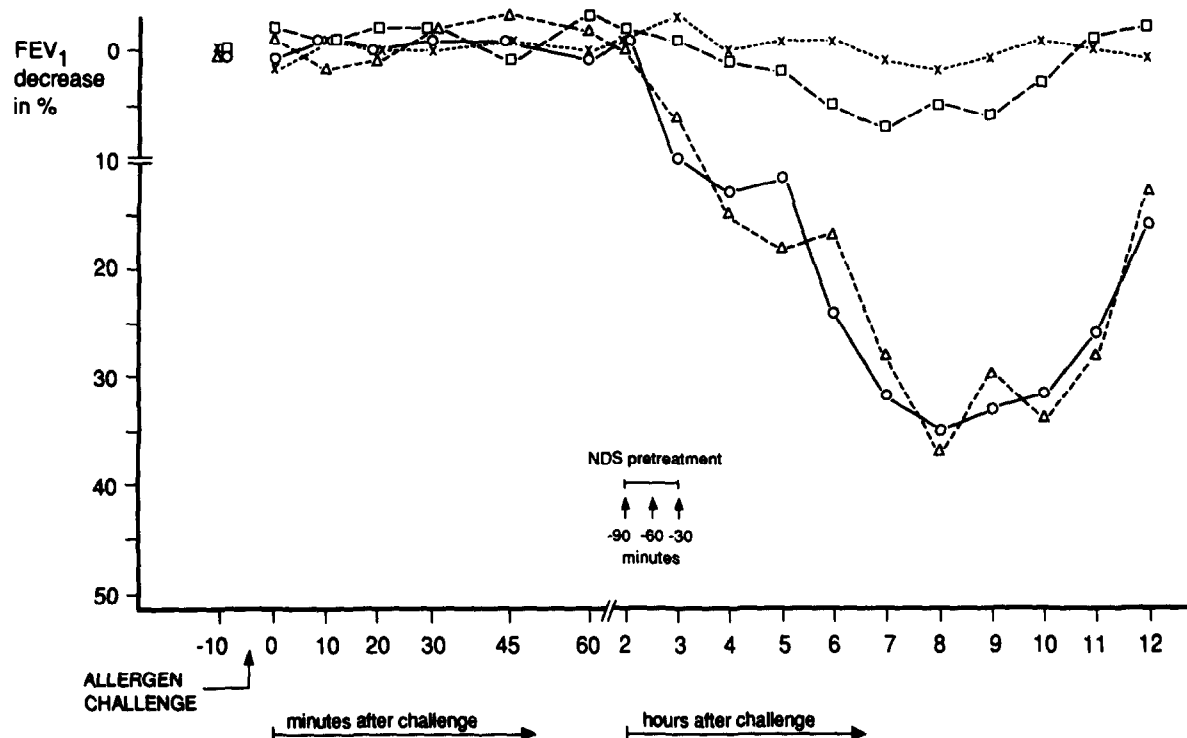


FIG. 1. Isolated late asthmatic response (ILAR) to allergen challenge and the protective effects of NS in five patients. The mean percentage change in FEV₁ values calculated from the nonpretreated ILARs (○), the ILARs pretreated with NS (□) and with placebo (△), and from PBS control challenges (x).

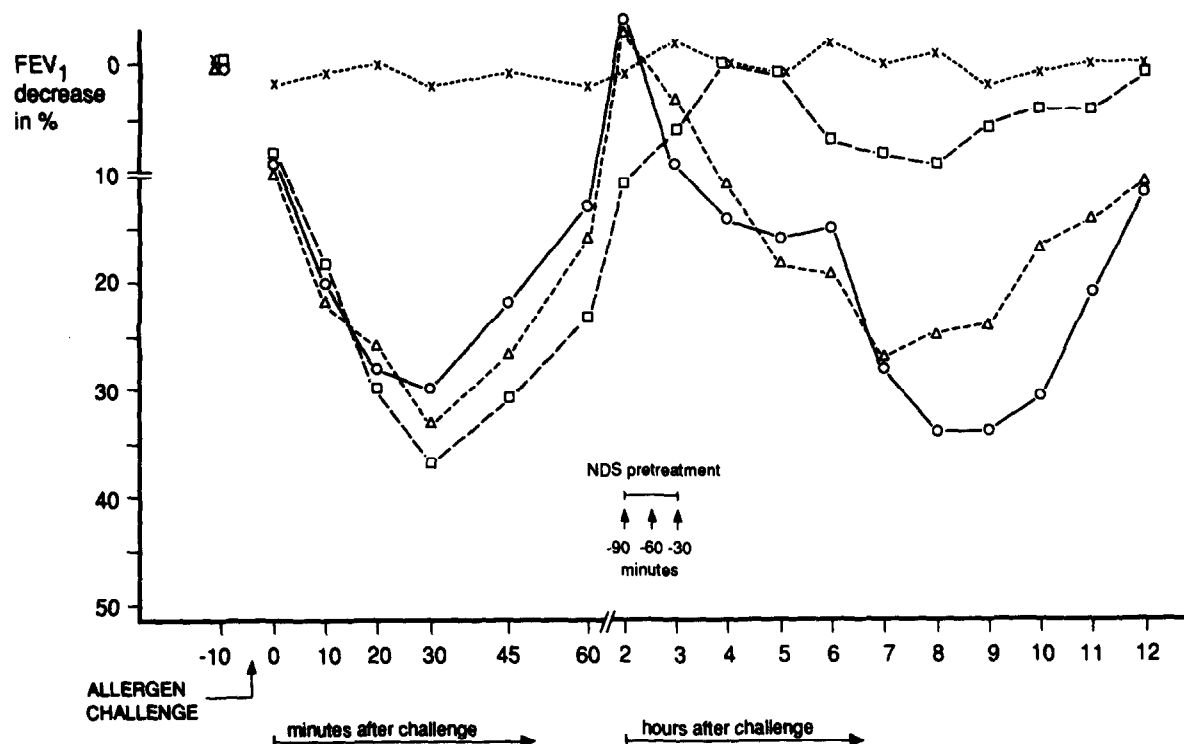


FIG. 2. Dual late asthmatic response (DLAR) to allergen challenge (DLAR, immediate + late) and the protective effects of NS in nine patients. The mean percentage change in FEV₁ values calculated from the nonpretreated DLARs (○), the DLARs pretreated with NS (□) and with placebo (△), and from PBS control challenges (x).

TABLE III. Mean maximum percentage falls from prechallenge baseline FEV₁ during LAR due to allergen inhalation

Type of response	Study treatment	Baseline FEV ₁ (L)	Max % fall in FEV ₁
Dual LAR (<i>n</i> = 9)	No treatment	3.44 ± 1.12	37.1 ± 5.15
	Placebo	3.43 ± 1.10	28.5 ± 19.05
	NS	3.42 ± 1.08	11.4 ± 15.00
Isolated LAR (<i>n</i> = 5)	No treatment	3.22 ± 0.85	39.7 ± 7.81
	Placebo	3.20 ± 0.86	42.1 ± 16.48
	NS	3.20 ± 0.88	14.3 ± 11.29
All LARs (<i>n</i> = 14)	No treatment	3.36 ± 1.01	38.0 ± 6.07
	Placebo	3.35 ± 0.99	33.4 ± 18.77
	NS	3.34 ± 0.98	12.4 ± 13.40
Treatment difference (all):			
Standard deviation (df)		0.067	14.93
<i>p</i> Value			
Treatment order		0.78	0.18
Treatment effect		0.78	0.003*
(Treatment × responder type)		(0.84)	(0.40)

**p* < 0.01.

the consecutive bronchial challenges. The concentration of allergen producing a significant asthmatic response (FEV₁ fall ≥ 20%) of any type was considered to be a final dose and was also used for the protection tests. All bronchial challenges, both nonpretreated and pretreated, were supplemented by recording of various bronchial and general complaints and symptoms (Table II).

Control test with PBS

A control test with PBS was performed in all patients 3 days before the bronchial challenge with allergen, and the spirometric values were recorded for up to 56 hours. Results of the control test were considered to be negative when the changes in FEV₁ values varied within 8% with respect to baseline values.

Drug administration and schedule of protection tests

Nedocromil sodium (Tilade) (1 puff = 2 mg NS) and placebo were used in the form of a metered pressurized aerosol. Each treatment consisted of 2 puffs administered at 3 time intervals (90, 60, and 30 minutes) before the predicted onset of the LAR.

The protection tests with NS and with placebo were performed with a time interval of 5 days, in the same way and according to the same schedule as that used for the nonpretreated allergen challenge. The design of the study was randomized, double-blind, crossover, placebo-matched.

Statistical analysis

The FEV₁ before allergen challenge (baseline value) and the percentage change in FEV₁ after challenge were compared by analysis of variance with patient,

treatment, and study day as factors. The maximum percentage fall in FEV₁ during the LAR was taken as the primary variable, although the fall in FEV₁ at each time point was also analyzed. The nonparametric method of Koch²⁴ was used to confirm the primary analysis. The possible difference in treatment effects on the LAR between isolated and dual responders was examined by means of analysis of variance with treatment and responder type as factors. A two-tailed significance level of 5% was used throughout. A *p* value of less than 0.05 was considered to be statistically significant, a *p* value of less than 0.01 to be distinctly significant, and a *p* value of less than 0.001 to be highly significant.

RESULTS

The 14 patients developed 14 LARs to allergen challenge. Each LAR began between 4 and 6 hours, reached its maximum between 8 and 10 hours, and resolved within 12 to 24 hours after the allergen challenge. Five patients demonstrated an isolated late response (Fig. 1), and nine showed a dual late response, which is a combination of an immediate and a late response (Fig. 2). All LARs were highly significantly positive as compared with PBS control challenge (*p* < 0.001). During the nonpretreated LAR, the mean maximum percentage fall in FEV₁ was 38.0% (range, 25.6% to 50.0%) from a mean baseline value of 3.36 L (range, 1.60 to 5.30 L) (Table III). There were no withdrawals from the study. Some patients needed rescue therapy, a single inhalation of 100 µg salbutamol, when their FEV₁ fell below 50% during the nonpretreated LAR or during admin-

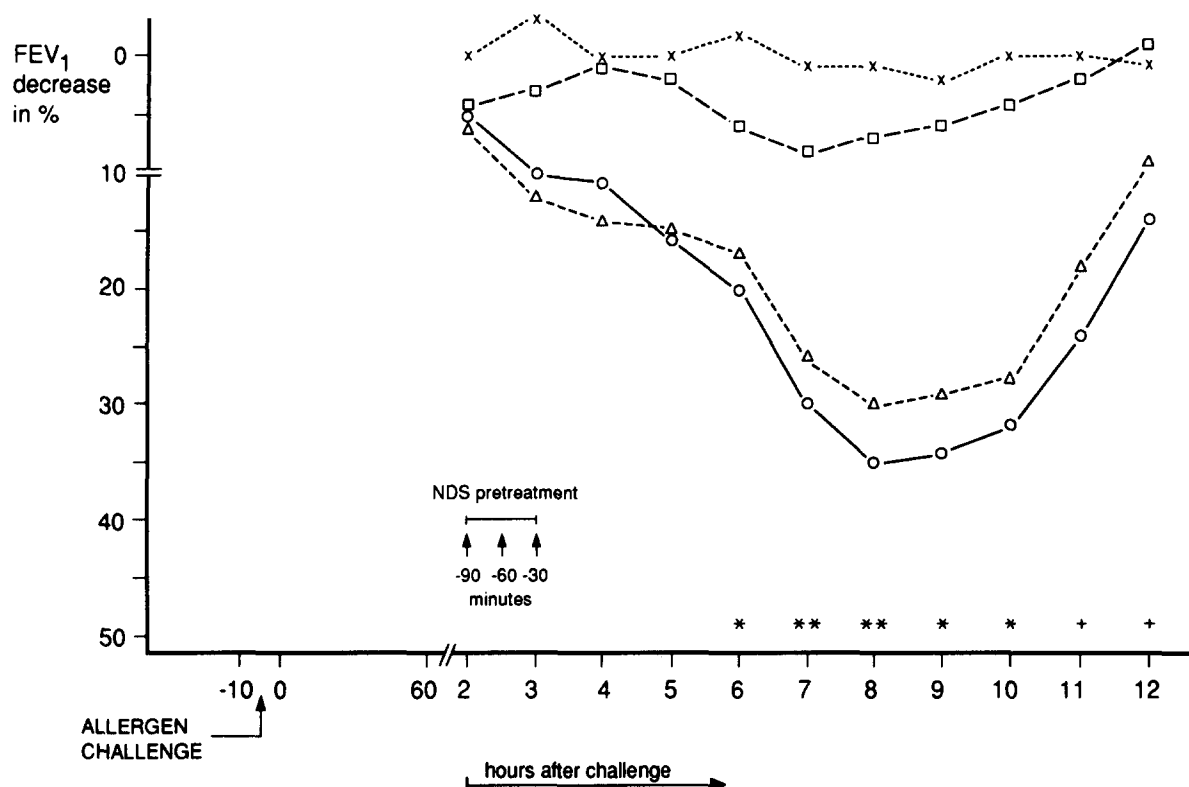


FIG. 3. LAR to allergen challenge and the overall protective effects of NS in all 14 patients. The mean percentage change in FEV₁ values calculated from the nonpretreated LARs (○), the LARs pretreated with NS (□) and with placebo (△), and from PBS control challenges (x). Significance of the protective effects of NS on the LAR as compared with those of placebo: * $p < 0.05$; ** $p < 0.01$; + $0.05 < p < 0.1$.

istration of placebo. The values obtained after salbutamol administration were excluded from the analysis. None of the patients required rescue therapy after administration of NS. All PBS control challenges were significantly negative ($p > 0.2$) (Figs. 1 and 2).

NS prevented 12 cases of LAR (86%) significantly ($p < 0.01$) and was ineffective in two LAR cases (14%) ($p \geq 0.05$). The mean maximum percentage fall in FEV₁ during the LAR pretreated with NS was significantly reduced ($p = 0.003$) and showed an improvement of 21.0% as compared with placebo (95% confidence interval = 8.6% to 33.2%). Only three of the 14 patients demonstrated a fall in FEV₁ greater than 20% after NS pretreatment. This protection lasted over the entire time course of the LAR, showing significance ($p < 0.05$) whether viewed from 6 to 10 hours after allergen challenge or from 2.5 to 6.5 hours after the first treatment dose, allowing for individual variation in the time of onset.

Placebo demonstrated slight protective effects in two cases of LAR (14%) ($p \leq 0.05$) and was

fully ineffective in 12 cases of LAR (86%) ($p > 0.05$). Eleven of the 14 patients showed a maximum fall in FEV₁ of more than 20% after placebo treatment.

The overall protective effects of NS on the LAR as compared with those of placebo were found to be highly statistically significant ($0.002 < p < 0.01$) (Fig. 3). The treatment differences were slightly greater in patients with isolated LAR. However, analysis of variance indicated no significant differences between the two LAR types in comparing test treatments (Table III).

In all patients studied, the bronchial, as well as general, complaints accompanying the nonpretreated LAR were distinctly prevented by NS but not by placebo (Table II).

DISCUSSION

The LAR may play an important role in bronchial asthma and may be responsible for failure of the usual treatment in these patients.^{6, 7, 12}

The views on the pathophysiologic and immunologic mechanisms leading to the LAR, how-

ever, vary. Some investigators have suggested involvement of the late hypersensitivity and IgG antibodies in the LAR.^{1, 6, 7, 12, 25, 26} Other investigators have presumed that immediate hypersensitivity, mediated by IgE antibodies, on involvement of mast cells (and/or basophils), may play the main role in the LAR.^{13, 14} Others have assumed that various combinations and modifications of the above-mentioned mechanisms may be involved.^{12, 27-29}

In our opinion, the LAR should be regarded as a clinical phenomenon, defined by the appearance of bronchoconstriction, accompanied by other symptoms and changes, within 4 to 12 hours after allergen exposure.^{6, 7, 10-12} Although the pathogenetic and immunologic mechanisms leading to the LAR could be different, the late type of hypersensitivity should be regarded as one of the possibly involved mechanisms but certainly not the only one.^{6, 7, 11, 12} Nevertheless, evidence has been provided for involvement of various inflammatory mechanisms including various cell types, chemical mediators, and chemotactic factors in clinical LAR.* This very complex topic is extensively discussed elsewhere.^{6, 7, 12, 34, 35}

Some investigators have presumed the role of IAR in the development of the LAR and postulated that the LAR is preceded by an IAR.^{3, 14} Our results, which demonstrate unequivocally the existence of an isolated form of LAR, do not agree with this presumption.^{5-7, 10-12, 17}

Because the LAR has been recognized as an important clinical phenomenon, its pharmacologic modulation has also become a current topic.^{6, 7, 10-12, 31} The effects of various drugs have been studied with varying results.† The antihistamines, anticholinergics, and theophylline derivatives did not demonstrate any significant effects; β -agonists were slightly effective; while disodium cromoglycate (DSCG), corticosteroids, and NS showed significant protective effects on the LAR.‡

The comparative studies of the effects of DSCG and topical corticosteroids (beclomethasone dipropionate [BDP] and budesonide) on the LAR are not numerous.^{1, 10, 11, 31} In our previous studies, both DSCG and BDP/budesonide significantly prevented the LAR ($p < 0.01$), with small differences.^{10, 11} In patients who had the dual response, however, the IAR was prevented significantly by DSCG ($p < 0.01$), although not by BDP

($p > 0.05$).⁹⁻¹¹ Similar results were also reported by Pepys and Hutchcroft¹ and Cockcroft and Murdock.³¹

In our preliminary studies the patients with dual asthmatic response were pretreated with DSCG or BDP/budesonide for 48 hours before allergen challenge. DSCG, the administration of which was finished 10 minutes before the allergen challenge, only prevented significantly the IAR ($p < 0.05$), but not the LAR ($p > 0.05$). Although if administration was continued up to 12 hours after the allergen challenge, it prevented significantly both the IAR ($p < 0.02$) and the LAR ($p < 0.05$).^{37, 41} In contrast, BDP/budesonide demonstrated significant protective effects on the LAR ($p < 0.01$) without any differences between the two treatment schedules, but they did not affect the IAR at all ($p > 0.05$).^{41, 42}

We also compared the effects of a single dose of DSCG or budesonide on the LAR, administered either before or after allergen challenge (before the onset of LAR), in patients with dual asthmatic response. (Some of these data have not yet been published). DSCG administered 30 minutes before allergen challenge prevented the IAR significantly ($p < 0.05$) but did not affect the LAR ($p > 0.05$). The DSCG given 1, 2, 3, or 4 hours after the challenge did not prevent the LAR ($p > 0.05$). The budesonide administered 30 minutes before the allergen challenge prevented the LAR significantly ($p < 0.01$) but did not affect the IAR ($p > 0.05$). Budesonide administered 1, 2, or 3 hours after the allergen challenge prevented the LAR significantly ($p < 0.05$).^{41, 42}

The differences in the pharmacologic modulation of the early (IAR), as well as the late (LAR) phase, of asthmatic response by DSCG and BDP/budesonide, administered at various time intervals with respect to the allergen challenge, would suggest involvement of different mechanisms in the early and in the late phase.^{4-7, 12} The allergen exposure may activate the mechanisms that cause the IAR, or those that lead to the LAR, or both the groups simultaneously, resulting in parallel appearance of IAR and LAR. With respect to these preliminary results, the so-called "dual asthmatic response" may perhaps be considered as an appearance of two independent responses.

The differences in the protective effects of DSCG and topical corticosteroids (BDP/budesonide) on the particular types of asthmatic response may be explained by their different pharmacologic effects.^{12, 43-45} The effects of DSCG on

*References 6, 7, 10-13, 16, 26, 27, 30-36.

†References 10, 11, 15, 17, 21-23, 36-42.

‡References 10, 11, 15, 17, 21-23, 31, 36, 37, 39-42.

the IAR, as well as on the LAR, could be explained by the ability of DSCG to protect mast cells and basophils from degranulation and subsequent release of mediators.⁴³ The glucocorticosteroids possess a manifold antiinflammatory activity including effects on the regulation of cyclic adenosine monophosphate, cyclic guanosine monophosphate, prostaglandins, various chemotactic factors, complement parts, and vasoactive kinins, as well as effects on various cell types (e.g., eosinophils, neutrophils and platelets).^{44, 45}

NS has a number of unique pharmacologic properties, including antiinflammatory effects.^{18-20, 22, 46} In animal in vitro studies, NS protected mast cells from degranulation²⁰ and inhibited the secretory response of neutrophils.¹⁹ In animal in vivo studies, NS inhibited the release of histamine, leukotriene C₄ and prostaglandin D₂ from mast cells in bronchoalveolar lavage and was more potent in preventing antigen-induced bronchoconstriction in primates than DSCG.¹⁸ In guinea pigs NS that was inhaled 15 minutes before the antigen challenge inhibited both IAR and LAR, whereas salbutamol inhibited the IAR only. When inhaled 6 hours after the challenge, NS prevented LAR significantly, but salbutamol prevented LAR only partially. NS also reduced accumulation of eosinophils, but not of neutrophils, in bronchoalveolar lavage from these animals.²⁰

In the human in vitro studies NS inhibited histamine release from human "chopped lung" and inhibited activation of eosinophils and neutrophils.¹⁹ NS also prevented the chemotactic factor-induced activation of eosinophils and neutrophils (formyl-methionyl-leucyl-phenylalanine) by means of inhibition of expression of their C3b and IgG (Fc) membrane receptors,⁴⁶ the eosinophil activation induced by platelet activating factor, and the increase in IgG-dependent release of leukotriene C₄ from human eosinophils.⁴⁶ NS, like DSCG, was able to inhibit the sepharose-C3b-induced protein release from eosinophil granules.⁴⁷ NS also prevented the IgE-dependent activation of human alveolar macrophages, blood monocytes, and platelets and the release of their mediators.⁴⁸ NS showed a higher inhibitory activity on the human mast cells from bronchoalveolar lavage and from dispersed lung fragments than DSCG.^{49, 50}

In human in vivo studies, when administered 30 minutes before the challenge, NS inhibited the bronchoconstriction caused by inhaled sulfur dioxide, fog,^{51, 52} and adenosine, but not by methacholine.⁵³ In bronchial challenge studies with an-

tigen, NS demonstrated significant protection on both IAR and LAR, when administered in a single dose of 4 mg before the challenge.²¹ NS inhibited the IAR to allergen challenge in patients with asthma to a higher degree than DSCG, when administered in a single dose of 2 or 4 mg, 30 minutes, 2 hours, or 3 hours before the challenge.^{54, 55} The safety of NS and a high measure of tolerability have also been confirmed.^{38, 51} In long-term clinical trials, NS demonstrated a significant reduction in the requirement for steroids in patients with bronchial asthma.³⁸

It can be concluded that NS shares some pharmacologic effects with DSCG, especially those concerning activities expressed on mast cells and eosinophils. NS also demonstrates antiinflammatory effects, which are similar to those of the glucocorticosteroids. This unique position of NS should be stressed, following the recognition of the key role of inflammatory events in the pathogenesis of asthma and the clinical importance of the LAR.^{6, 7, 10-13, 16, 33}

According to our preliminary data and other investigators' findings, DSCG administered before the predicted onset of LAR was not able to inhibit this response.^{40, 41} Results of this study show that NS, given 30 to 90 minutes before the expected onset, inhibited the LAR significantly. These data may indicate the differences in the effects and properties between DSCG and NS, and they also implicate the involvement of different mechanisms in IAR and those in LAR. From a practical point of view, these results demonstrate an effective prophylaxis of LAR by a single dose of NS given even after allergen exposure. NS might therefore be considered a very promising drug for the control and preventive treatment of allergic bronchial asthma.

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