

Respiratory pathophysiologic responses

Beclomethasone given after the early asthmatic response inhibits the late response and the increased methacholine responsiveness and cromolyn does not

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Background: Single doses of inhaled beclomethasone or inhaled cromolyn, given before allergen inhalation, inhibit allergen-induced late asthmatic responses (LARs) and increased airway responsiveness ($\Delta \log$ methacholine PC_{20}). We hypothesized that when given 2 hours after allergen, beclomethasone might work better than cromolyn.

Methods: In 10 patients with mild, stable, atopic asthma with LARs or $\Delta \log PC_{20}$ or both, we performed a double-blind, double-dummy, random-order trial comparing a single dose of inhaled beclomethasone (500 μ g), cromolyn (20 mg), and placebo, administered 2 hours after allergen challenge on LAR and $\Delta \log PC_{20}$.

Results: The treatment effect on LAR was significant ($p < 0.001$). The LAR after beclomethasone ($7.3\% \pm 6.1\%$) was significantly less than after cromolyn ($20.4\% \pm 15.2\%$) or placebo ($26.4\% \pm 8.2\%$); cromolyn was not different from placebo. There was a borderline treatment effect on $\Delta \log PC_{20}$ ($p = 0.056$) with beclomethasone (0.12 ± 0.31) less than placebo (0.37 ± 0.39) but not less than cromolyn (0.34 ± 0.18).

Conclusion: Beclomethasone (500 μ g) administered 2 hours after allergen challenge markedly inhibited the LAR and had a small effect on allergen-induced airway responsiveness. Cromolyn (20 mg) was not effective on maximal LAR; a small effect on the early part of the LAR was suggested. (*J ALLERGY CLIN IMMUNOL* 1993;91:1163-8.)

Key words: Beclomethasone, cromolyn, allergen inhalation tests, late asthmatic response, allergen-induced increase in airway responsiveness

We have previously demonstrated that single doses of the inhaled prophylactic medications, beclomethasone dipropionate and cromolyn sodium, administered before allergen inhalation, will significantly inhibit

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Abbreviations used

EAR: Early asthmatic response

LAR: Late asthmatic response

FEV₁: Forced expiratory volume in 1 second

PC₂₀: Provocation concentration (methacholine) causing a 20% fall in FEV₁

$\Delta \log PC_{20}$: Change in log₍₁₀₎ methacholine PC₂₀ after allergen inhalation—a measure of allergen-induced increase in airway responsiveness

both the late asthmatic response (LAR) to antigen and allergen-induced increase in histamine airway responsiveness.¹ By contrast, a single dose of the beta-agonist albuterol did not significantly influence the late

sequelae.¹ The current investigation was carried out to investigate the effect on allergen-induced late sequelae when single doses of beclomethasone and cromolyn are administered 2 hours after the allergen challenge. The hypothesis being tested was that the inhaled corticosteroid, being actively antiinflammatory, might be more effective in blocking these late sequelae than the cromolyn, which appears to be "prophylactically" antiinflammatory.

METHODS

Subjects

Ten subjects with atopic asthma were recruited from the Chest Clinics at the Royal University Hospital in Saskatoon, Saskatchewan, and at the Ambrose Cardiorespiratory Unit, McMaster University Medical Centre in Hamilton, Ontario, as well as from advertisements. The subjects had atopic asthma with mild, well-controlled asthma requiring either no therapy or only occasional inhaled beta-agonist at the time of study. The forced expiratory volume in 1 second (FEV_1) was greater than 70% of predicted. All subjects had at least one allergen to which there was a moderate-to-high response both clinically and on allergy prick skin testing. A dose finding allergen challenge produced an LAR 10% or greater ($n = 2$) or a twofold or greater fall in provocation concentration causing a 20% fall in FEV_1 (PC_{20}) ($n = 1$) or both ($n = 7$). This investigation was approved by the ethics committees at the universities, and signed informed consent was obtained.

Methacholine inhalation tests

Airway responsiveness to methacholine was measured by means of a standardized method.² Aerosols were nebulized by a Bennett Twin (Puritan-Bennett Corp., Carlsbad, Calif.) jet nebulizer calibrated to deliver an output of 0.13 ml/min with a flow rate of 4.5 L/min. Three milliliters of room temperature solutions were added to the vial. The FEV_1 was initially measured in triplicate. The diluent, sterile isotonic saline solution was inhaled for 2 minutes of tidal breathing through the mouth, and measurement of the FEV_1 was repeated at 30 and 90 minutes. Doubling concentrations of methacholine, from 0.03 mg/ml to 32 mg/ml were inhaled for 2 minutes at 5-minute intervals; the FEV_1 measurement was repeated at 30 and 90 seconds, and if necessary, at 3 minutes after each inhalation. The change in FEV_1 was measured from the lowest postsaline FEV_1 to the lowest postmethacholine FEV_1 , and the test was continued until the FEV_1 had fallen by 20% or more or until the top concentration had been administered. Methacholine PC_{20} was then calculated by linear interpolation of the last two data points.³

Dose-finding allergen inhalation tests

Allergen inhalation tests were performed as previously reported.^{1,4} Aerosols were generated by a Wright (Aerosol

Products Ltd., London, England) nebulizer calibrated to deliver 0.13 ml/min at an airflow rate of 6.5 L/min. The aerosol was nebulized into a Hans Rudolph valve (Hans Rudolph, Inc., Kansas City, Mo.) and then via a mouthpiece to the subject. The exhalate was collected on the expiratory side of the valve with two ventilator circuit filters (BB-50T; Paul Biomedical Inc., Fajardo, Puerto Rico). On a control day, the allergen diluent, isotonic buffered saline with 0.5% phenol, was inhaled for 2 minutes of tidal breathing on three occasions at 10-minute intervals. The FEV_1 was measured initially in triplicate, 10 minutes after each inhalation, and then after the last inhalation every 10 minutes for 1 hour, every 30 minutes for the second hour, and then hourly up to 7 hours after inhalation. On this day duplicate prick skin tests with the allergen to be used for inhalation were performed with dilutions of 1:8 up to 1:1024 or greater from the stock solution of aqueous extract. The skin test end point was defined as the smallest concentration producing a mean wheal diameter of 2 mm. Methacholine PC_{20} was measured at 7 hours. The predicted allergen PC_{20} was calculated from the methacholine PC_{20} and from the skin test end point.⁴ Appropriate concentrations for multiple allergen inhalations were then frozen in single use 3 ml aliquots in vials compatible with the Wright nebulizer.

On the second day allergen inhalation was done by use of the identical technique. The starting concentration was generally five concentrations below the prediction to allow for a minimum of three inhalations for safety for all the repeat studies. Doubling concentrations of allergen were inhaled for 2 minutes at 10-minute intervals until the FEV_1 had fallen by 12% or greater at 10 minutes. The highest initial FEV_1 and the highest postinhalation FEV_1 measurements were used to determine the percent change. The FEV_1 was measured after the last allergen concentration for 7 hours as on the control day. Methacholine PC_{20} was measured at 7 and 30 hours after the allergen challenge.

Study design

Three further allergen inhalation tests were performed with use of three concentrations of allergen. On all three occasions the subjects received the identical dose of allergen. Nine of these subjects received the same final dose of allergen as on the dose-finding allergen challenge, whereas one subject (no. 8) received 50% of the dose administered on the dose-finding allergen challenge because of large early asthmatic responses (EARs) and LARs on the initial allergen challenge. The repeat allergen challenges were done at 1 week or longer intervals, and were done when the baseline FEV_1 was within 10% of previous challenges, when the methacholine PC_{20} measured the afternoon before was back to within one concentration of baseline, and at a time when there had been no natural allergen exposure for greater than 4 weeks, and no respiratory tract infection for greater than 4 weeks. Medications were administered in the interval between the EAR and LAR 2 hours after the completion of the allergen inhalation (after the 2-hour spirogram). This

TABLE I. Anthropometric data

Patient no.	Age	Sex	Ht. (cm)	Wt. (kg)	Rx	Allergen	Allergen Conc.	FEV ₁ (L)	Methacholine PC ₂₀ mg/mL
1	22	F	160	55.5	Nil	Grass	1:256	3.85	32
2	31	M	173	73	A	Grass	1:8	3.96	13
3	18	F	171	63.6	Nil	Cat	1:16	4.02	6.5
4	26	F	160	64	Nil	Cat	1:8	3.41	3.9
5	37	M	180	70	Nil	HDM	1:64	3.41	3.2
6	30	F	180	60	A	HDM	1:256	2.64	1.6
7	32	M	169	72.7	A	Cat	1:16	3.52	1.6
8	24	F	168	56	A	HDM	1:16	3.36	0.72
9	22	F	157	54	A	Cat	1:8	3.03	0.34
10	43	M	170	64	F	Grass	1:512	2.62	0.25

A, Albuterol (prn); F, fenoterol (prn); HDM, house dust mite (*D. farinae*).

TABLE II. EAR, LAR, and $\Delta \log PC_{20}$

Patient no.	EAR (% fall FEV ₁)				LAR (% fall FEV ₁)				$\Delta \log PC_{20}$			
	Nil	P	CS	BDP	Nil	P	CS	BDP	Nil	P	CS	BDP
1	32	29	46	41	10	7	4	4	0.49	0.46	0	-0.15
2	20	23	25	22	16	44	24	11	0.20	-0.06	0.42	-0.23
3	23	13	9	31	14	6	9	7	0.22	0.23	0.35	0.11
4	31	20	34	38	12	10	13	0	0.49	-0.26	0.19	-0.06
5	29	33	40	31	39	40	38	11	0.86	0.77	0.30	0.45
6	13	24	21	19	44	50	50	21	0.58	0.82	0.64	0.54
7	8	25	14	19	17	20	11	5	0.75	0.83	0.44	0.45
8	(37)	24	21	19	(29)	44	29	8				
9	34	23	40	26	4	6	4	0	0.44	0.18	0.32	0.23
10	32	33	36	45	39	37	22	6	0.32	0.36	0.36	-0.22
Mean	24.7	24.7	28.6	29.1	21.7	26.4	20.4	7.3	0.48	0.37	0.34	0.12
SD	9.3	6.0	12.3	9.7	14.8	18.2	15.2	6.1	0.22	0.39	0.18	0.31
n	9	10	10	10	9	10	10	10	9	9	9	9

P, Placebo; CS, cromolyn sodium; BDP, beclomethasone dipropionate.

was 2 hours before the beginning of the LAR in the eight subjects in whom this could be identified (exceptions, no. 1 and no. 9 who had minimal or no LAR). Beclomethasone (500 μ g) and cromolyn (20 mg) were administered in a double-blind, double-dummy manner by inhalation. On one occasion two puffs from a beclomethasone inhaler (250 μ g per puff) and four puffs from a placebo inhaler were taken; on the other occasion four puffs of cromolyn (5 mg per puff) and two puffs from a placebo inhaler were taken. Double placebo inhalations were administered at 2 hours on the final allergen challenge day in a single-blind manner so that an unmedicated allergen challenge was available before and after the two active treatments for comparison of responses in 9 of the 10 subjects.

Spirometry was followed for 5 hours after the medications were administered. Methacholine PC₂₀ was measured at 7 and 30 hours. A number of subjects with large LARs did

not have 7-hour PC₂₀ measurements made at all (subjects 5 and 6) or on occasion (subjects 2 and 8). Accordingly, only the 30-hour values were used for analysis in subjects 2 through 10, and the 7-hour value was used in subject 1, a patient with no LAR but a reproducible fall in methacholine PC₂₀ at 7 hours.

Analysis

The EAR was defined as the maximum percent reduction in FEV₁ during the first hour after allergen challenge, and the LAR was defined as the maximum percent reduction in FEV₁ occurring between 3 and 7 hours after allergen challenge. Allergen-induced increase in airway responsiveness to methacholine was defined as the $\Delta \log PC_{20}$ from preallergen to postallergen challenge. An index of variability of the two

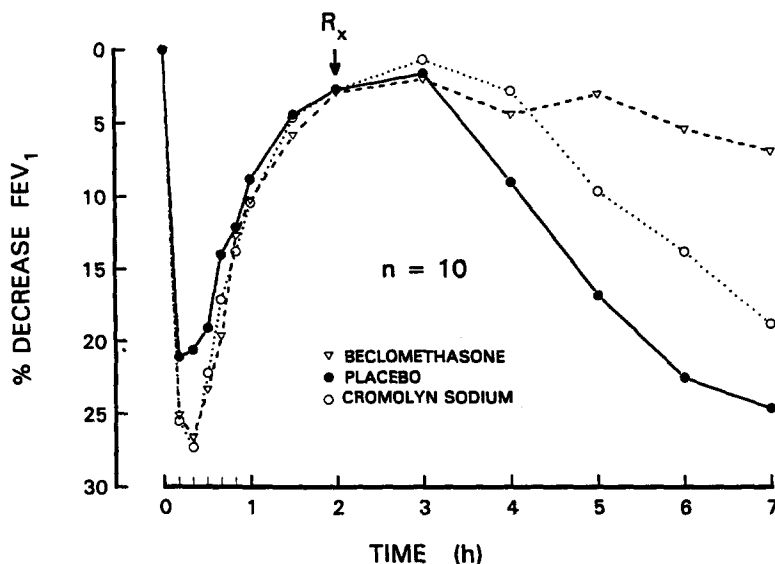


FIG. 1. Airway response to allergen. FEV₁ (% fall) on vertical axis and time (hr) on horizontal axis. Medications (beclomethasone [500 µg], cromolyn [20 mg], or placebo) administered at 2 hours (arrow).

unmedicated tests (days 2 and 5) was calculated; $100 \times \text{mean difference} / \text{mean of the tests}$.

The three measurements (EAR, LAR, and $\Delta \log PC_{20}$) for the three treatments (placebo, beclomethasone, cromolyn) were analyzed with use of an analysis of variance (ANOVA)⁵; differences between individual treatments were assessed with Scheffe's test.⁶ Because of an apparent trend for a mild cromolyn effect, a repeated measures ANOVA⁷ was applied to the curves from 3 to 7 hours to examine for a subtle effect of treatment.

RESULTS

The anthropometric data, baseline FEV₁, methacholine PC₂₀, and allergen used for inhalation are given in Table I. All 10 subjects completed the study. There was one major protocol violation. Subject no. 8 had a moderately severe LAR on the placebo day followed by nocturnal symptoms partially refractory to albuterol and took inhaled corticosteroid before measurement of the 30-hour methacholine PC₂₀. Consequently, 10 subjects were available for analysis of EAR and LAR, but only nine subjects were available to assess $\Delta \log PC_{20}$. Individual values for EAR, LAR, and $\Delta \log PC_{20}$ after all four allergen challenges are shown in Table II.

Reproducibility of the unmedicated allergen challenge response (dose-finding allergen test and placebo day) could be assessed in nine of the 10 subjects. The EAR varied by less than 50% in eight of the nine subjects (variability, 36%), the LAR by less than 50% in seven of the nine subjects (variability, 26%) and $\Delta \log PC_{20}$ by less than 1 doubling concentration (i.e.,

<0.3) in six of nine subjects (variability, 46%) (Table II). This is similar to variability noted previously.¹

The mean data for FEV₁ change after allergen challenge on the 3 days is shown in Fig. 1; no significant difference occurred in the EAR on any of the 3 days. ANOVA of the LAR revealed a highly significant treatment effect ($p < 0.001$). The LAR after beclomethasone ($7.3\% \pm 6.1\%$) was significantly less than the LAR after either cromolyn ($20.4\% \pm 15.2\%$) or placebo ($26.4\% \pm 18.2\%$) ($p < 0.05$). The LAR during the cromolyn period was not significantly different from the LAR during the placebo period. Individual data revealed that the LAR was reduced by 50% compared with placebo after the beclomethasone treatment in eight of the 10 individuals and after cromolyn treatment in none of the 10 individuals.

For the nine individuals in which it could be assessed $\Delta \log PC_{20}$ is given in Table II. ANOVA for all nine subjects revealed a borderline treatment effect ($p = 0.056$) with the beclomethasone $\Delta \log PC_{20}$ being lower than the placebo $\Delta \log PC_{20}$ and no other differences approaching significance. Two subjects did not demonstrate a fall in PC₂₀ on the placebo day. When these two subjects were omitted (subjects 2 and 4), and the analysis was repeated on the remaining seven subjects, there was a significant treatment effect ($p = 0.015$), with the only significant difference being beclomethasone $\Delta \log PC_{20}$ being less than the placebo $\Delta \log PC_{20}$. Individual data revealed a 50% reduction in $\Delta \log PC_{20}$ compared with placebo in four of nine subjects with beclomethasone and in two of nine subjects with cromolyn.

Although there was no difference at any individual time point, the repeated measures ANOVA showed the 3- to 7-hour curve for cromolyn to be significantly different from placebo ($p < 0.05$).

DISCUSSION

These data indicate that 500 μ g beclomethasone administered after the EAR reduces the LAR by an average of almost 70%, having greater than 50% protection in eight of 10 patients studied. A more variable and less significant effect on allergen-induced increase in airway responsiveness to methacholine was evident. Cromolyn sodium (20 mg) administered at the same time did not influence the maximum LAR or $\Delta \log PC_{20}$ when compared with placebo. When the late response curve from 3 to 7 hours was examined, it appeared the early portion (3 to 5 hours) was shifted to the right, and a repeated measures ANOVA showed this curve to be significantly different from placebo.

Previous studies have indicated that single dose inhaled corticosteroids,^{1, 8} cromolyn sodium,^{1, 9} and nedocromil,¹⁰ when given before allergen exposure, can significantly ameliorate the late asthmatic "inflammatory" sequelae. Under natural circumstances, patients are likely to not use their prophylactic medications until after exposure and the development of symptoms. This investigation was therefore carried out to assess single doses of these medications administered after allergen challenge and after development of symptoms in an effort to mimic more closely a common clinical situation. The preinvestigation hypothesis was that beclomethasone should prove more effective than cromolyn when used in this fashion. This appears to be confirmed by the investigations.

The apparent discrepancy between the major effect on the LAR and variable and smaller effect on $\Delta \log PC_{20}$ was initially somewhat of a surprise on the basis of similar inhibition of the two in several previous studies.^{1, 8-10} However, allergen-induced airway hyperresponsiveness can appear as early as 2 hours and is probably uniformly present (in those who demonstrate this feature) by 3 hours.^{11, 12} Both allergen-induced increase in airway responsiveness and the LAR are thought to be a result of airway inflammation on the basis of animal studies and circumstantial evidence in humans.¹³⁻¹⁵ Because allergen-induced airway hyperresponsiveness, however, both precedes and outlasts the LAR,^{11, 12, 16} it has been postulated to be a more sensitive indicator of inflammation. However, it is possible that different aspects of the inflammatory response may be responsible for the two phenomena, thus leading to the possibility of a differential response to pharmacologic agents of these two inflammatory sequelae. Indeed, indomethacin has been shown to

partially ameliorate $\Delta \log PC_{20}$ without influencing LAR.¹⁷ In this study corticosteroids appear to have the reverse effect, being more effective in inhibiting the LAR than $\Delta \log PC_{20}$.

To our knowledge few comparable data exist in the literature. Pepys et al.¹⁸ noted in one subject that cromolyn administered before and every 3 hours after allergen challenge was more effective than cromolyn administered only before allergen challenge in inhibiting the LAR. In the same subject when cromolyn was administered only after allergen challenge, it was less effective than cromolyn administered only before allergen challenge and only showed slight inhibition of LAR.¹⁸ Booij-Noord et al.¹⁹ administered cromolyn before the LAR and every 3 hours in six subjects and found no change in LAR. Mattoli et al.²⁰ studied five children sensitive to house dust mite and administered two doses of nebulized cromolyn (20 and 40 mg) 3 hours after allergen challenge. The effect on the LAR was similar to that demonstrated in this study, with a significant delay in the onset of the LAR but no change in the eventual magnitude of the LAR.²⁰ This was true for both doses of cromolyn, with a dose response being evident. In the study by Mattoli et al.,²⁰ however, a large protective effect was seen on $\Delta \log PC_{20}$; this was not seen in our study. The reasons for the difference are unclear. Mattoli's subjects had a larger $\Delta \log PC_{20}$ than those in our study; this may have altered the protective effect of cromolyn. The doses of cromolyn in the two studies are difficult to compare. Twenty milligrams from a metered-dose inhaler is likely equivalent to or larger than 20 mg administered from a continuous nebulization system (the method of inhalation in Mattoli's study was not specified) without a breathhold, even on a milligram per kilogram basis. Therefore dose differences do not appear important in explaining differences. The timing of our administration was 1 hour earlier (2 hours before LAR) when compared with the study by Mattoli et al.²⁰ It is possible that these methodologic differences explain the differences between their results and ours. In contrast to the human data, Hutson et al.²¹ showed a major inhibition of LAR in guinea pig sensitized to ovalbumin when cromolyn was inhaled 6 hours after allergen, before the LAR; in this study cromolyn inhibited eosinophil influx at 72 hours but not neutrophil influx at 17 hours.²¹

We are unaware of any corticosteroid studies in humans. In guinea pigs sensitized to ovalbumin, neither budesonide nor cromolyn administered 1.5 or 6 hours after allergen challenge inhibited the LAR measured 20 hours after allergen provocation.²²

In summary, 500 μ g of beclomethasone administered 2 hours after allergen challenge significantly inhibited the LAR and significantly but less effectively

inhibited the increased methacholine responsiveness. Cromolyn (20 mg) had a small effect on the early portion of the LAR but did not affect the maximal LAR or the increased airway responsiveness to methacholine.

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