

Theophylline attenuation of airway responses to allergen: Comparison with cromolyn metered-dose inhaler

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Background: The purpose of this study was to compare the protection afforded by individualized doses of theophylline and a cromolyn metered-dose inhaler (MDI) during allergen challenge.

Methods: The study design was randomized, double-blind, and crossover. Responses to inhaled allergen were measured in 16 subjects with allergic asthma (age range, 18 to 35 years) after 7 days of treatment with either placebo, once daily slow-release theophylline producing a mean $\pm$ SD serum concentration of 16 ± 5 μ g/ml during the late phase, or 2 mg of cromolyn administered by MDI four times daily. Forced expiratory volume in 1 second was measured at frequent intervals, and airway responsiveness to histamine was measured before and 3 hours after allergen challenge.

Results: The mean $\pm$ SD maximum decrease in forced expiratory volume in 1 second during the late phase was $30\% \pm 14\%$ during placebo treatment, $16\% \pm 13\%$ during theophylline treatment, and $13\% \pm 14\%$ during cromolyn treatment (placebo vs theophylline and cromolyn, $p = 0.0001$; theophylline vs cromolyn, $p = 0.1$). The geometric mean fold increase in airway responsiveness was 3.0 ± 1.7 during placebo treatment, 1.7 ± 1.7 during theophylline treatment, and 1.5 ± 1.6 during cromolyn treatment (placebo vs theophylline and cromolyn, $p = 0.0001$; theophylline vs cromolyn, $p = 0.1$).

Conclusions: Theophylline, when administered once daily as a slow-release formulation, was as effective as cromolyn, administered four times daily through an MDI, in attenuating airway responses to inhaled allergen. The protection afforded by both treatments, however, was modest when compared with the results of similar studies with inhaled corticosteroids or other cromolyn formulations that deliver more drug to the lungs than the MDI available in the United States. (*J ALLERGY CLIN IMMUNOL* 1995;95:505-14.)

Key words: Theophylline, cromolyn, allergic asthma, antiinflammatory

The efficacy of theophylline as a prophylactic agent in the treatment of chronic asthma has been demonstrated in several studies.¹ Also, there is

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Abbreviations used

FEV ₁ :	Forced expiratory volume in 1 second
MDI:	Metered-dose inhaler
PC ₂₀ :	Provocative concentration causing a 20% fall in FEV ₁
PD ₂₀ :	Provocative dose causing a 20% fall in FEV ₁

evidence that it provides a clinically significant additive benefit when administered with inhaled corticosteroid therapy.^{2,3} However, improvement in the clinical course of chronic asthma caused by theophylline appears disproportionately greater than the modest bronchodilating effect of this drug,^{2,4,5} suggesting that there may be an additional mechanism of action in chronic asthma.⁶⁻⁸

Although there are conflicting data in the literature,⁹ evidence indicates that theophylline attenuates the late-phase response^{7, 8, 10-12} and allergen-induced increase in airway responsiveness.^{12, 13} Two recent studies demonstrated that these actions are related to antiinflammatory effects of theophylline.^{7, 8} In addition, studies in animals indicate that the bronchodilatation and broncho-protective actions of theophylline are mediated by entirely different mechanisms.⁶

Cromolyn is the prototype antiallergic drug for suppressing the early- and late-phase responses to allergen and the allergen-induced increase in airway responsiveness.¹⁴ These effects, however, were demonstrated in studies with cromolyn Spincaps (20 mg/cap; Fisons Corp., Rochester, N.Y.), nebulizer solution (20 mg/2 ml), or a high-potency metered-dose inhaler (MDI) available outside the United States (10 mg/2 puffs); such formulations deliver an order of magnitude more cromolyn to the lungs than the MDI currently prescribed in the United States (2 mg/2 puffs*).^{15, 16}

There is no information on whether the MDI formulation of cromolyn available in the United States, at the recommended dose of 2 mg four times daily, delivers enough drug to the lungs to attenuate the response of the airways to inhaled allergen, and how this regimen compares with theophylline, a drug that has both bronchodilator and antiinflammatory actions. We therefore conducted a double-blind, randomized, placebo-controlled study to answer these questions.

METHODS

The study was approved by the University of Florida Institutional Review Board, and all subjects gave written informed consent.

Subject selection

Twenty-one nonsmoking, otherwise healthy young adults (ages 18 to 35 years) were selected for study on the basis of the following criteria:

1. A well-defined history of intermittent or mild chronic asthma not requiring continuous use of medication and increased asthmatic symptoms after exposure to cats or house dust mite that correlated with positive epicutaneous skin test results
2. Forced expiratory volume in 1 second (FEV₁) greater than 65% of the predicted value for age, height, race, and gender
3. A 20% decrease in FEV₁ after administration of less than 8 mg/ml inhaled histamine (i.e., a provocative concentration of histamine less than 8 mg/ml)
4. A dual response to inhaled allergen consisting of at least a 20% decrease in FEV₁ during the first hour and a 15% decrease 4 to 8 hours after allergen challenge
5. At least a twofold decrease in the provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) 3 hours after inhaled allergen
6. The ability to discontinue use of antihistamines for a minimum of 5 days (astemizole, 6 weeks) and to withhold inhaled albuterol for 6 hours

None of the subjects were taking inhaled, oral, or intranasal corticosteroids, intranasal cromolyn, or inhaled ipratropium before or during the study.

Medication administration

Study medications were administered in a double-blind, randomized, crossover design for 7 days before each study day. Theophylline was administered as Uni-Dur (Key Pharmaceuticals, Kenilworth, N.J.), a more slowly absorbed formulation of Theo-Dur (Key Pharmaceuticals), and cromolyn was administered as Intal MDI (1 mg/puff, Fisons Corp., Rochester, N.Y.). To achieve double-blinding, a double-dummy technique was used. Subjects took tablets and used MDI as follows:

1. Theophylline tablets every morning and placebo MDI, 2 puffs four times daily
2. Placebo tablets every morning and cromolyn MDI, 2 puffs (2 mg) four times daily
3. Placebo tablets every morning and placebo MDI, 2 puffs four times daily

A closed-mouth technique, without a spacer device, was used for administration of the MDI. Subjects held their breath for 10 seconds after each puff with a 1-minute interval between puffs.

Placebo tablets (identical in appearance to Uni-Dur) and placebo MDI (identical in appearance to Intal) were supplied by the respective manufacturers. Before randomization, the dose of slow-release theophylline tablets was slowly titrated, as tolerated, over a 9-day period. The final dosage was adjusted to achieve an 8-hour postdose steady-state serum theophylline concentration within the 10 to 20 µg/ml therapeutic range. On the basis of this titration, a mean dose of 712 mg/day (range, 600 to 1200 mg/day) was used in the double-blind portion of the study. After randomization, subjects took one half the number of theophylline or placebo tablets for the first 3 days of each treatment regimen and then the full dose for the remaining 4 days to circumvent transient theophylline side effects.

Subject adherence to each treatment regimen was confirmed by an unblinded pharmacist at the beginning of each double-blind study day by serum theophylline concentration measurement and change in MDI canister weight.

*Although this product contains 1 mg/puff, the Food and Drug Administration requires the manufacturer to label the product as delivering 0.8 mg/puff to the patient to account for loss of drug in the mouthpiece.

TABLE I. Prestudy FEV₁, histamine PC₂₀, and allergen dose on the allergen screening day among the 16 subjects who completed the study

Subject No.	Age	Gender	Allergen	Allergen dose*	Prestudy Histamine PC ₂₀ (mg/ml)	Prestudy FEV ₁ (% predicted)
2	25	M	DF	36	3.0	77
3	21	M	DF	31	5.4	93
4	20	F	DF	13	1.2	89
5	18	F	DP	58	6.9	97
6	22	M	DF	38	0.8	103
7	26	F	DF	26	0.8	86
8	35	F	DF	36	4.0	98
11	20	F	DF	13	2.2	107
12	20	F	DP	3	1.4	78
13	32	F	Cat hair	73	4.2	90
14	22	M	DF	10	2.7	79
15	18	F	Cat hair	1206	2.4	87
17	21	M	DP	4	0.8	93
19	19	M	DF	4	1.1	82
20	28	F	Cat hair	140	4.3	103
21	21	F	DF	4	1.0	88
Mean	23			24†	2.1†	91
SD	5			5	2.1	9

DF, *Dermatophagoides farinae*; DP, *D. pteronyssinus*.

*The cumulative dose of allergen during the last hour of the screening allergen challenge, in RAST-Standardized Allergy Units, required to produce a 20% decrease in FEV₁ during the early phase (PD₂₀).

†Geometric mean ± geometric SD.

On each study day, theophylline or placebo tablets were administered after measurement of baseline FEV₁ and histamine PC₂₀, and cromolyn or placebo was administered by MDI 30 minutes before allergen challenge. The cromolyn or placebo MDI dose was repeated twice at approximately 4-hour intervals, just before the second histamine challenge (3 hours after allergen), and 8 hours after the beginning of the study day, for a total of three doses on each study day.

Study protocol

Allergen challenge study days were at least 7 days apart. After 7 days of treatment, subjects reported to the Asthma Research Laboratory between 7:00 and 8:00 AM for measurement of lung function and histamine PC₂₀. The study continued only if adherence to the treatment regimen was confirmed, FEV₁ was at least 90% of the prestudy value, and histamine PC₂₀ was no lower than 1 twofold dilution from the geometric mean of previous baseline measurements. These precautions were taken so that allergen would not be administered to a subject who was still experiencing increased airway responsiveness from a previous allergen challenge. If these conditions were not met, the study day was postponed, the blinded treatment regimen was continued, and the baseline evaluation was repeated at 7-day intervals until the criteria were met or 4 weeks had elapsed.

When the baseline criteria were met and FEV₁ re-

turned to within 90% of baseline value for that study day (usually less than an hour after histamine challenge), the treatment regimen was administered and the allergen challenge was started 30 minutes later. Fresh solutions of standardized allergen extract diluted in sterile phosphate-buffered saline were prepared each study day, and the same dose of allergen was administered on each of the 3 double-blind study days so that the stimulus for the late phase would be the same (Table I). Three hours after the nadir of the early phase, the histamine challenge was repeated to measure the allergen-induced increase in airway responsiveness. This time point was selected because, in our experience, histamine challenges cannot be performed safely at 24 hours in many subjects because FEV₁ may be less than 65% of predicted value; whereas 3 hours after the early phase, FEV₁ has usually returned to baseline value and the late phase has not begun. Airway responsiveness to histamine precedes the onset of the late phase, and at 3 hours after allergen challenge, PC₂₀ values are similar to those obtained at 24 hours in subjects who manifest the late response.¹⁷

During the early phase, the protocol provided for the administration of isoproterenol through an MDI, if the subject requested a bronchodilator to relieve symptoms. Administration of an ultrashort-acting β -agonist at this time point is unlikely to have altered the response to histamine at 3 hours or the magnitude of the late phase¹⁸

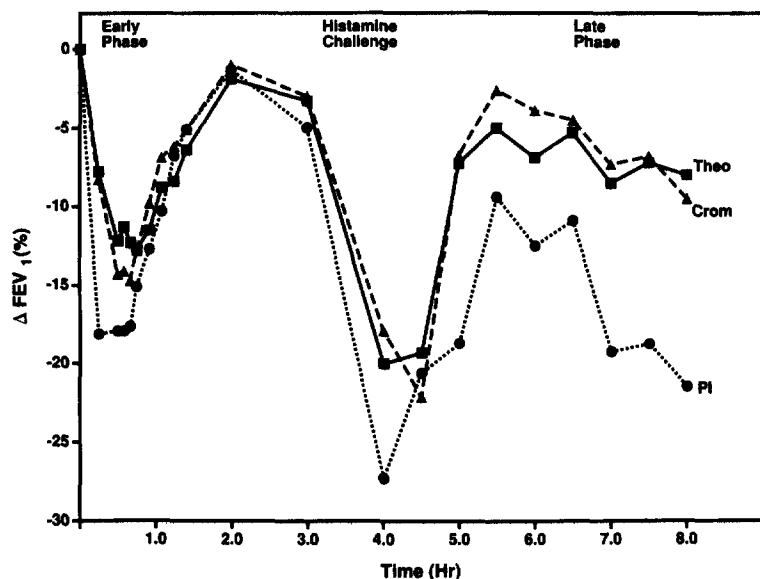


FIG. 1. The time course of mean change in FEV₁ after allergen challenge on each study day, expressed as a percent of the prechallenge value. For clarity, the standard deviations of each mean value were omitted. The three treatments are identified as follows: *PI* = placebo (●—●), *Theo* = theophylline (■—■), and *Crom* = cromolyn (▲—▲). The mean maximum decreases in FEV₁ during the early and late phases shown in the figure are smaller than values reported in the text and Table II. The figure represents the mean change for the group at each time point, whereas the maximum decreases reported in the text and Table II were the mean of the individual maximum decreases, which occurred at different times.

because there is little bronchoprotective effect 1 hour after administration.¹⁹ During the late phase, nebulized albuterol (2.5 mg in 3 ml of saline solution) was administered to relieve symptoms on the request of the subject or when FEV₁ decreased below 40% of predicted value.

Pulmonary function measurements

Spirometry was performed, with the subject sitting and wearing a nose clip, by using a Collins water-sealed spirometer attached to an Eagle II microprocessor and printer (W.E. Collins, Braintree, Mass.). The spirometer was calibrated daily with a 3 L syringe. Lung function was measured every 10 minutes during the first hour, hourly before and after the 3-hour histamine challenge, and at 30-minute intervals until the nadir of the late phase was passed (Fig. 1). For measurement of baseline or postdiluent FEV₁, the best of three maneuvers within 100 ml of each other was selected. During histamine and allergen challenges, only a single measurement was obtained to avoid tiring the subject. During hourly and half-hourly measurements after allergen challenge, spirometry was performed in duplicate, and the highest value was selected if both values were within 100 ml of each other. When necessary, additional maneuvers were performed, up to six times, to obtain consistent results. FEV₁ was expressed as a percent of predicted value for age, height, race, and gender.²⁰

Histamine challenges

A modification of the tidal breathing method described by Cockcroft and Murdock¹⁴ was used to measure airway responsiveness to histamine. The modifications consisted of use of a mouthpiece instead of a mask and attaching a filter (Respirgard II; Marquest, Englewood, Colo.) to the exhaust port to prevent histamine from entering the ambient air. The aerosol was generated by a Wright nebulizer (Roxon Medi-Tech, Montreal, Quebec, Canada), driven by oxygen at 50 psi. The flow rate was regulated by a precision flow meter (Rotometer; Fischer and Porter, Warminster, Pa.), and the nebulizer was calibrated weekly to produce an output of 0.13 ml/min. Sterile phosphate-buffered saline was used as a diluent for the histamine solutions and as the diluent control. Subjects inhaled each solution for 2 minutes, and single spirometric maneuvers were performed at 30, 90, and 180 seconds. After inhaling diluent, subjects inhaled twofold increasing concentrations of histamine at 5-minute intervals until FEV₁ decreased by 20% or more. During the first screening histamine challenge, the initial concentration was 0.03 mg/ml. Thereafter, the initial concentration before allergen challenge was 1 twofold dilution below the previously measured PC₂₀. Three hours after allergen challenge, the initial concentration of histamine was one fifth of the PC₂₀ measured at the beginning of that study day.

The change in FEV₁ was calculated as follows:

$$\% \Delta \text{FEV}_1 = \frac{(\text{FEV}_1 \text{ after diluent}) - (\text{lowest FEV}_1 \text{ after histamine})}{(\text{FEV}_1 \text{ after diluent})} \times 100$$

The histamine PC₂₀ was interpolated from the last 2 data points on the plot of log concentration and percent decrease in FEV₁.

Allergen challenge

The initial dose of allergen on the screening day (expressed as RAST-standardized allergy units) was 3 twofold dilutions of the lowest concentration that produced a 2 mm wheal during epicutaneous skin testing of serial dilutions of the allergen. A twofold increase in dose was administered at 15-minute intervals until FEV₁ decreased by 20% or more from the prechallenge value. FEV₁ was measured 5, 10, and 15 minutes after each allergen dose. Because the initial allergen challenge often took more than an hour, the provocative dose causing a 20% fall in FEV₁ (PD₂₀) during the early phase was calculated from the cumulative dose administered during the 60 minutes before the early phase (Table I). During double-blind study days, for added safety, the PD₂₀ was divided into 2 aliquots and administered at 10-minute intervals. If the first aliquot produced a decrease of more than 15% in FEV₁, 2 puffs of isoproterenol were administered by MDI, and the remaining aliquot was administered when the FEV₁ returned to at least 80% of baseline value. Administration of a very short-acting β -agonist during the early phase does not affect the magnitude of the late phase¹⁸ and allows the safe administration of the same allergen stimulus for the late phase on each study day. Because there is little or no bronchoprotective effect 1 hour after administration of isoproterenol,¹⁹ administration during the early phase is unlikely to affect histamine PC₂₀ 3 hours later.

Theophylline serum concentrations

Blood was obtained for measurement of theophylline serum concentrations during all three treatment regimens before the morning dose and at the maximum decrease in FEV₁ during both the early- and late-phase responses. The concentration was measured in duplicate by polarization immunoassay (Abbott TDx; Abbott Laboratories, Diagnostic Div., Irving, Texas). The coefficients of variation for between-day precision over a 30-day period were less than 5% at concentrations of 7.0, 12, and 26 $\mu\text{g/ml}$ ($n = 12$).

Data analysis

The degree of protection against allergen-induced late-phase response for each active treatment was calculated as follows:

$$\% \text{ Protection} = \frac{\text{FEV}_1 \text{ placebo} - \text{FEV}_1 \text{ active}}{\text{FEV}_1 \text{ placebo}} \times 100$$

where FEV₁ represents the maximum percent decrease in FEV₁. The allergen-induced increase in airway responsiveness to histamine was calculated from the log₂ of the ratio of the PC₂₀ measured at the beginning of the study day and 3 hours after allergen as follows:

$$\Delta \text{PC}_{20} = \frac{\text{PC}_{20} \text{ 0 hr}}{\text{PC}_{20} \text{ 3 hr}}$$

This ratio represents the fold decrease in PC₂₀ at 3 hours (i.e., the fold increase in airway responsiveness).

Statistical analysis was performed on the following outcome measures: baseline FEV₁, baseline log₂ PC₂₀, maximum percent decrease in FEV₁ during the early phase, maximum percent decrease in FEV₁ during the late phase, and log₂ PC₂₀ ratio at 3 hours after allergen challenge. Analysis of variance was used to determine whether the order of treatment affected the results and to compare the mean values for each outcome measurement. A contrast variables approach,²¹ which gives specific error terms for the contrasts of interest, was used to determine whether the effect of the placebo was different from that of theophylline and cromolyn and whether theophylline and cromolyn produced a different outcome. Lastly, the McNemar test was used to determine whether the number of interventions with inhaled β -agonists differed between treatments.

The null hypothesis was rejected at $p < 0.05$. All data, except PC₂₀ values, are expressed as means $\pm$ SD. PC₂₀ and PC₂₀ ratio are expressed as a geometric mean and geometric standard deviation, because the data required log transformation to obtain a normal distribution.

RESULTS

Of the 21 subjects enrolled in the study, 17 completed all treatments. Four subjects were dropped from the study; one required a prednisone burst, a second performed spirometry inconsistently, a third could not meet the criteria for baseline histamine PC₂₀ before each study day, and a fourth subject did not adhere to the protocol. Data from a fifth subject was excluded from the analysis because he did not have a late-phase response during placebo treatment. Thus data were analyzed for 16 subjects (Table II). The treatment order did not significantly affect any of the outcome measures. The mean baseline histamine PC₂₀ measured at the beginning of each study day was slightly higher during both theophylline and cromolyn treatment than during placebo treatment ($p = 0.02$), but there was no significant difference between the two active treatments (Fig. 2). Just before allergen challenge, there were small but significant differences in FEV₁ among all three treatments: $88.8\% \pm 10.2\%$ of predicted value with placebo, $93.9\% \pm 10.2\%$ with theophylline (mean serum concentration, $16.2 \pm 4.9 \mu\text{g/ml}$),

TABLE II. Maximum decrease in FEV₁ during early and late phases and increased airway responsiveness to histamine after allergen challenge on each study day

Subject No.	Maximum % ↓ in FEV ₁ during early phase			Maximum % ↓ in FEV ₁ during late phase			Airway responsiveness (fold ↓ histamine PC ₂₀)*		
	Placebo	Theo	Crom	Placebo	Theo	Crom	Placebo	Theo	Crom
2	16.6	5.0	16.4	16.6	6.2	6.3	1.5	1.0	1.4
3	23.7	10.6	3.9	39.2	8.8	3.0	10.3	4.6	1.1
4	20.5	13.0	22.5	13.2	10.5	7.0	2.2	1.1	1.3
5	29.2	7.5	10.2	20.2	16.2	6.3	6.2	3.2	1.0
6	17.2	23.3	13.4	17.2	18.0	3.5	1.8	1.5	1.3
7	31.2	21.7	4.1	33.0	17.5	1.6	3.0	1.5	1.5
8	29.1†	31.3	28.1	20.1	6.6	7.0	3.5	1.4	1.3
11	29.0†	34.1	34.5	36.1	37.2	23.8	3.0	5.0	3.4
12	35.8	23.1†	18.5	55.9‡	50.8‡	54.5‡	ND§	ND§	4.3
13	23.3	3.2	0	19.3	6.8	0	4.6	1.0	1.5
14	22.6†	36.2†	33.7†	14.8	13.8	16.2	2.1	1.9	1.0
15	8.5	13.7	20.1†	33.9	18.0	18.4	2.2	1.0	1.0
17	58.1†	23.4†	26.0	47.7‡	25.6	22.9	ND§	2.6	2.7
19	31.2	9.7	16.8	48.6‡	10.8	9.1	2.7	1.8	1.0
20	9.4	7.9	11.1	24.5	1.2	7.0	4.1	1.0	1.8
21	23.6†	4.2	7.4	39.7	8.5	19.2	2.1	1.6	1.4
Mean	25.6	16.7	16.5	30.0	16.0¶	12.9¶	3.0	1.7¶	1.5¶
SD	11.6	10.9	10.5	13.6	12.7	13.5	1.7	1.7	1.6

↓, Decrease; *Theo*, theophylline; *Crom*, cromolyn; *ND*, not done.*PC₂₀ 0 hr ÷ PC₂₀ 3 hr: The larger the ratio, the greater the decrease in PC₂₀ at 3 hours (i.e., the greater the increase in airway responsiveness). Mean ratios are expressed as geometric means ± geometric SD.†Subjects who received 2 puffs of isoproterenol because FEV₁ decreased by more than 20% after first aliquot of allergen was administered.‡Subjects treated with 2.5 mg of nebulized albuterol during the late phase because FEV₁ decreased below 40% of predicted value.§Histamine challenge could not be performed because FEV₁ was less than 65% of predicted value.||*p* = 0.01 (placebo vs theophylline and cromolyn) and *p* = 0.9 (theophylline vs cromolyn).¶*p* = 0.0001 (placebo vs theophylline and cromolyn) and *p* = 0.1 (theophylline vs cromolyn).

and 91.1% ± 9.3% with cromolyn (placebo vs theophylline and cromolyn, *p* = 0.0001; theophylline vs cromolyn, *p* = 0.009).

Both cromolyn and theophylline decreased the early- and late-phase responses to inhaled allergen (Fig. 1). The maximum decrease in FEV₁ during the early phase was 25.6% ± 11.6% with placebo, 16.7% ± 10.9% with theophylline, and 16.5% ± 10.5% with cromolyn (placebo vs theophylline and cromolyn, *p* = 0.01; theophylline vs cromolyn, *p* = 0.9) (Table II). Isoproterenol was required during allergen challenge in five subjects receiving placebo, in three subjects receiving theophylline, and in two subjects receiving cromolyn (*p* = 0.1). During the late phase, the maximum decrease in FEV₁ was 30% ± 14% with placebo, 16% ± 13% with theophylline (mean serum concentration, 16.4 ± 4.6 μg/ml), and 12.9% ± 13.5% with cromolyn (Table II). The late phase was significantly greater during

placebo administration than during either active treatment (*p* = 0.0001), but there was no significant difference between theophylline and cromolyn (*p* = 0.10). We estimate with 80% confidence that the power to detect a 20% difference between cromolyn and theophylline was 91% with a sample size of 16 subjects and α = 0.05. Nebulized albuterol was required for a decrease in FEV₁ below 40% of predicted value by three subjects receiving placebo, but by only one subject receiving theophylline and cromolyn treatments (one subject required rescue medication during all three treatments). The protection against allergen-induced late-phase response was 44% during theophylline treatment and 58% during cromolyn treatment (*p* = 0.08).

Attenuation of the allergen-induced increase in airway responsiveness to histamine followed the same pattern as the late-phase response (Fig. 2). The fold decrease in PC₂₀ 3 hours after

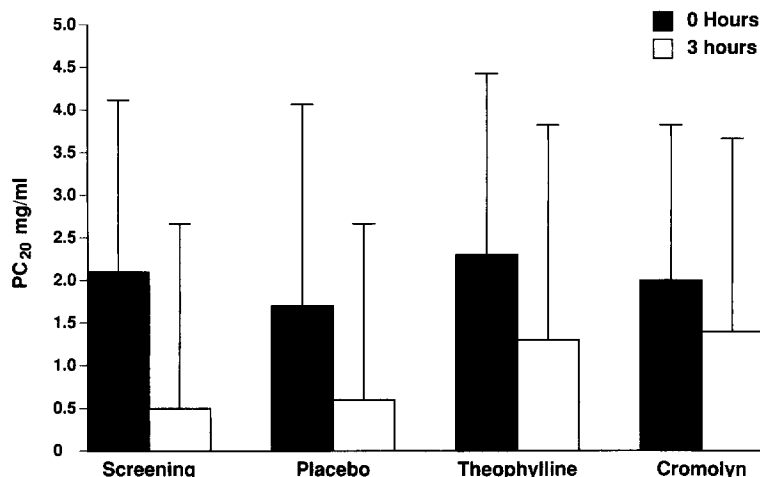


FIG. 2. The geometric mean $\pm$ geometric SD inhaled histamine PC₂₀ measured at the beginning of each study day 1 to 2 hours before allergen challenge (0 hours, ■) and 3 hours after the nadir of the early phase (3 hours, □). The "screening" day represents the histamine PC₂₀ values obtained before and after allergen challenge without pretreatment.

allergen was 3.0 ± 1.7 with placebo, 1.7 ± 1.7 with theophylline, and 1.5 ± 1.6 with cromolyn (placebo vs theophylline and cromolyn, $p = 0.0001$; theophylline vs cromolyn, $p = 0.1$) (Table II). We estimate with 80% confidence that the power to detect a twofold difference in the change in airway responsiveness between theophylline and cromolyn was 97% with a sample size of 16 subjects and $\alpha = 0.05$.

There was no significant difference in the frequency of adverse effects among the three treatments.

DISCUSSION

The results of this study demonstrate that theophylline, administered in individualized doses once daily as a slow-release formulation, is as effective as cromolyn, administered four times daily through an MDI, in attenuating the response of the airways to inhaled allergen. Both active treatments provided about 50% protection from the allergen-induced increase in airway responsiveness to histamine, as well as the late-phase response. However, the effects of both drugs were modest when compared with the results of previous studies of other formulations of cromolyn or inhaled corticosteroids in which nearly 100% protection was reported.¹⁴ Because the mean theophylline serum concentration during the late phase in this study was 16 $\mu\text{g/ml}$, greater than 50% protection cannot be safely obtained with theophylline. In contrast, administration of higher doses of cromolyn is likely to

provide greater protection without risk of adverse effects.

These data indicate that cromolyn administered by MDI (2 mg/2 puffs), the formulation most commonly prescribed in the United States, is less effective in this clinical model than other formulations of cromolyn. Because less than 1% of a swallowed dose of cromolyn is absorbed into the systemic circulation²² (i.e., cromolyn is not orally bioavailable), plasma concentrations and urinary excretion of the drug are undetectable after oral administration. However, after oral inhalation, cromolyn is absorbed into the systemic circulation¹⁶ and primarily excreted into the urine²³ and bile unmetabolized. The area under the plasma concentration–time curve^{15, 16} or the amount of the drug excreted into the urine²³ is directly proportional to the dose that reaches the systemic circulation and thus is an indicator of the amount of drug delivered to the lungs. Several studies have demonstrated that the peak plasma concentration and area under the plasma concentration–time curve correlate with the dose, inhalation technique, and clinical effect.^{15, 16, 24–26} Although there are no plasma concentration data from a crossover design study of all cromolyn formulations in the same subjects, the reported mean peak plasma concentrations from different studies were 43 ng/ml after administration of Spincaps (20 mg),¹⁵ 10 ng/ml after administration of nebulizer solution (20 mg),¹⁶ and 3 ng/ml after use of an MDI (2 mg/2 puffs).¹⁶ These data, along with the results of this

study, indicate that the MDI formulation available in the United States delivers an order of magnitude less cromolyn to the lungs than other formulations. This conclusion is supported by at least one long-term clinical study in children, which demonstrated that the MDI was less effective in controlling nocturnal symptoms than the Spincap formulation.²⁷ In addition, the 2 mg/2 puffs formulation did not reduce airway responsiveness in several long-term studies; whereas the 10 mg/2 puffs MDI available in Europe, the Spincap, and nebulizer solution all significantly improved this hallmark of chronic asthma.²⁸

The results for theophylline in this study are consistent with most previous reports demonstrating a modest attenuation of the late-phase response^{7, 8, 10-12} or the allergen-induced increase in airway responsiveness.^{12, 13} In contrast, Cockcroft et al.⁹ reported that theophylline did not significantly attenuate any of the responses to inhaled allergen, although a higher potency cromolyn MDI (10 mg/2 puffs) completely inhibited all of the responses. It is likely that their results differed from ours because of inadequate sample size (type II statistical error) and differences in study design. They studied only five subjects with a documented late-phase response, and airway responsiveness to methacholine was measured 24 hours after the last dose of Theo-Dur when serum concentrations would be very low. Also, the cromolyn dose in their study was five times higher than that in ours and was administered as a positive control in an unblinded and unrandomized manner. Thus Cockcroft et al.,⁹ often quoted as having proven that theophylline has only bronchodilator action, reached a specious conclusion.

It is unlikely that theophylline's attenuation of the airway responses to inhaled allergen is a consequence of functional antagonism (i.e., simply preventing the airway response by relaxing bronchial smooth muscle). Although theophylline produced bronchodilatation in this study, the differences in FEV₁ measured just before allergen challenge were trivial (3% greater than cromolyn, 5.7% greater than placebo) when compared with the degree of protection from allergen (almost 50%).

Although it can be argued that our subjects, whose mean FEV₁ was 91% of predicted value before the study, had little capacity for bronchodilatation, in fact, lung function increased during theophylline treatment in 14 of 16 sub-

jects, but there was no correlation between prestudy FEV₁ and percent increase during theophylline treatment. In two recent studies theophylline provided similar protection from allergen during the late phase at concentrations in the 5 to 10 µg/ml range,^{7, 8} which produced no bronchodilatation. In isolated guinea pig trachea, theophylline protects against constrictor stimuli without functional antagonism.²⁹ In vivo in the guinea pig, theophylline inhibits bronchoconstriction induced by allergen and leukotriene D₄ by the same mechanism but produces bronchodilatation by a different mechanism involving inhibition of an isoenzyme of phosphodiesterase.⁶ Thus bronchodilatation is unlikely to play an important role in theophylline attenuation of the responses to allergen.

The mechanism of action of theophylline on the late-phase response appears to relate to antiinflammatory effects rather than inhibition of mast cell release of mediators. Although theophylline has been shown to decrease the release of histamine during intranasal allergen challenge,³⁰ it does not suppress the cutaneous response to allergen,³¹ and in another study it attenuated the late-phase response to inhaled allergen but did not inhibit the early response, which is associated with mast cell release of mediators.¹⁰ In contrast, Ward et al.⁷ demonstrated that theophylline's protective effect on the late-phase response involves modulation of lymphocyte activity, and Sullivan et al.⁸ demonstrated that theophylline decreases allergen-induced increase and activation of eosinophils in bronchial mucosa. Also, Fink et al.³² have shown that both the number and activity of suppressor T cells in the peripheral blood are increased during long-term therapy with theophylline. In vitro theophylline has been used to functionally delineate helper and suppressor/cytotoxic T cells,³³ and it inhibits polymorphonuclear leukocyte activation and generation of leukotriene B₄.³⁴ In animal studies theophylline has been shown to reduce the number of neutrophils in bronchoalveolar lavage fluid during the late phase,³⁵ to decrease mucosal edema,³⁶ and to inhibit Calmette-Guérin bacillus-induced pulmonary inflammation.³⁷

The results of this study, when considered with other available data, have at least two implications. First, theophylline should not be classified as only a bronchodilator along with β-agonists and anticholinergics. Rather, it should be placed in a separate category as a prophylactic anti-

asthma agent with both bronchodilator *and* anti-inflammatory actions. Second, the 1 mg/puff MDI available in the United States delivers less cromolyn to the lungs than other formulations of this drug (e.g., Spincaps or nebulizer solution), which may have therapeutic implications in some patients.

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