

Effect of the oral leukotriene antagonist, ICI 204,219, on antigen-induced bronchoconstriction in subjects with asthma

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We studied the effect of a single oral dose of ICI 204,219 on subject response to bronchoprovocation and quantitative skin testing with standardized allergen (cat dander). Cat-allergic male subjects with asthma entered the double-blind, randomized, placebo-controlled, crossover study. Each subject received a 40 mg dose of ICI 204,219 or placebo on study days separated by at least 10 days. After dosing, each subject underwent bronchoprovocation with cat allergen until a provocative dose of allergen caused a 20% decrease in FEV₁ or a maximum dose of 30,000 AU/ml was reached. Fifteen subjects entered and 13 completed the study. No significant shift in the dose-response curve of the quantitative skin test occurred in any subject. A mean tenfold increase in the interpolated provocative concentration causing a 20% decrease in FEV₁ was observed between ICI 204,219 (6996 ± 3204 AU/ml) and placebo (460 ± 98 AU/ml). Eight of 12 subjects required more antigen to provoke a bronchoprovocation response after dosing with ICI 204,219 than that required with placebo (range, threefold to 30-fold), three demonstrated no difference (less than twofold), and one subject required less antigen after ICI 204,219 (sevenfold less). Area under the curve measurements were significantly different (p < 0.05) between ICI 204,219 and placebo for the fixed time from the end point of the allergen bronchoprovocation to 5 hours after provocation. In conclusion, this trial demonstrates that a single oral dose of ICI 204,219 antagonizes the bronchoconstriction induced by inhaled cat allergen. (J ALLERGY CLIN IMMUNOL 1992;89:1040-5.)

Key words: Leukotriene antagonist, ICI 204,219, asthma, allergen, bronchoprovocation

Peptide LTC₄, LTD₄, and LTE₄ are believed to play a major role in the pathogenesis of allergic asthma, and several studies have demonstrated the bronchoconstrictor effects of leukotrienes in humans.¹⁻⁴ Although the degree of response to leukotrienes varies between subjects with asthma and normal subjects,³ as does the degree of sensitivity between subjects with asthma and normal subjects to leukotrienes and methacholine,⁴ studies confirm that leukotrienes are potent bronchoconstrictors in humans. Studies have dem-

Abbreviations used

- LT: Leukotriene
- ECG: Electrocardiogram
- AU: Allergy units
- PC₂₀: Provocative concentration causing a 20% decrease in FEV₁
- PD₂₀: Provocative dose of allergen causing a 20% decrease in FEV₁

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onstrated that LTD₄, in particular, is a potent bronchoconstrictor with a rapid onset of action, a prolonged duration, and an effect on small and large airway function.^{3, 5, 6} Research with peptide leukotriene antagonists, drugs designed to inhibit biosynthesis or activity of leukotrienes at effector end organs, yielded several compounds that block leukotriene-induced bronchoconstriction and have therapeutic potential in allergic asthma. An example of these compounds is SKF 104,353, a potent antagonist of LTD₄

and LTE_4 . Clinical investigations are in progress to evaluate its potential as an aerosol therapy for the treatment of asthma.^{7,8} Another potent LTD_4 -receptor antagonist, MK-571, attenuated exercise-induced bronchoconstriction in a study of subjects with asthma.⁹

ICI 204,219, a potent oral leukotriene antagonist, inhibited LTD_4 -induced bronchoconstriction in a clinical trial with normal subjects.⁵ The encouraging safety and efficacy profile obtained from the LTD_4 -challenge trial prompted further investigation of ICI 204,219 in subjects with asthma. This study was conducted to investigate the antagonism of ICI 204,219 on standardized (cat dander) antigen-induced bronchoconstriction in subjects with bronchial asthma and to assess the safety of ICI 204,219 during an inhalation challenge.

METHODS

Subject selection and study design

Fifteen male subjects with asthma, between the ages of 18 and 50 years, participated in this double-blind, randomized, placebo-controlled, two-period, crossover study. Subjects who were selected for the study met the asthma criteria of the American Thoracic Society¹⁰ and were nonsmokers. None of the subjects had clinical signs or symptoms of airway obstruction or required concomitant medications, and all subjects had $\text{FEV}_1 \geq 65\%$ and a positive skin test to cat antigen. Subjects were instructed not to consume alcoholic beverages 1 week before the study or caffeinated products, or medication 12 hours before each dose of oral medication. All subjects gave their informed consent, and the study was approved by appropriate review boards.

Two weeks before the study, subjects provided a complete medical history and underwent physical examinations, 12-lead ECGs, clinical laboratory tests, blood tests for hepatitis B, urine drug screens, chest x-rays, pulmonary function tests, quantitative skin tests for histamine and cat antigen, and bronchoprovocation testing to cat dander. Physical examinations were repeated at check-in and before discharge for each study session. ECGs were repeated before and 24 hours after dosing and immediately after the bronchial challenge tests. Vital signs were recorded and subjective symptomatology interviews were conducted during each physical examination, before the bronchial challenge, and at 0, 1, 3, and 5 hours after peak response. Urine drug screens were repeated at check-in for each session. Clinical laboratory tests were performed before and 24 hours after dosing. Plasma samples were obtained after a peak bronchoprovocation response for analysis of blood levels of ICI 204,219.

Each subject participated in two study sessions, and each session was separated by 10 to 17 days. On the morning of study day 1 (for each session), subjects reported to the clinical research center in a fasted state and received a single oral 40 mg dose (two 20 mg tablets) of ICI 204,219 or identical placebo tablets. All subjects remained overnight for testing and monitoring procedures.

Allergen and histamine preparation

Freeze-dried allergen was reconstituted in 2.5 ml of sterile human serum albumin and diluted to a concentration of 100,000 AU/ml (0 dilution). The initial histamine concentration equaled 0.1 mg/ml histamine base. Dilutions were prepared before drug administration with sterile human serum albumin. Allergen dilution 1 was 30,000 AU followed by dilution 2 at 10,000 AU. This pattern was repeated to obtain dilutions 3 through 12. Identical ratios were used for histamine dilutions.

Skin testing

Quantitative skin tests for antigen and histamine were performed 3 hours after reaching peak bronchoprovocation. A series of intradermal injections (0.05 ml) of histamine and cat antigen were applied to the volar forearm. The skin test was observed for wheal and erythema reactions. After 15 minutes, the average diameter of the wheal and erythema was measured and recorded. The end point was defined as the highest concentration not to cause a reaction after 15 minutes. Response was determined quantitatively, in millimeters, as the sum of the longest orthogonally wheal and erythema diameters. A four-point response curve was generated for both antigen and histamine dilutions, including the end point and the next three higher concentrations.

Bronchial provocation test

Bronchial provocation tests were performed according to the guidelines of the American Thoracic Society.¹¹ A Rosenthal-French (Laboratory of Applied Immunology, Baltimore, Md.) nebulization dosimeter (0.6 sec per breath-activated solenoid valve), model 2A, was used with a DeVilbiss No. 646 nebulizer (DeVilbiss Co., Somerset, Pa.). Screening provocations began with the lowest antigen concentration to elicit a positive skin test.

At each study session, subjects were challenged 2 hours after receiving study medication. This 2-hour period was chosen because an LTD_4 challenge had been blocked completely in normal subjects 2 hours after a single 40 mg dose.⁵ Bronchoprovocation tests began at two antigen concentrations below the lowest concentration to cause a significant change from the diluent control during the screening provocation. The highest antigen concentration to produce a PC_{20} during screening was 300 AU/ml.

Each subject inhaled diluent followed by increasing concentrations of cat dander at 10-minute intervals. Five breaths of each dilution were delivered. Testing was terminated when a positive response occurred, as defined by a 20% reduction in FEV_1 , or when a maximum concentration (30,000 AU/ml) of cat dander was reached. The reduction in FEV_1 was calculated with the FEV_1 postdiluent bronchoprovocation as 100%. Subjects who did not respond by a 20% reduction in FEV_1 at 30,000 AU/ml were considered nonresponsive to cat dander for that period. The PD_{20} was determined by estimating the actual dose to produce a response (calculated as the number of breaths times the milliliters per breath times the allergen concentration).

Spirometry was performed 10 minutes after each chal-

TABLE I. Demographic characteristics

Subject	Age (yr)	Treatment period							
		Screen		ICI 204,219			Placebo		
		FEV ₁	FEV ₁ % predicted	Predose FEV ₁	2-hr Postdose FEV ₁	ICI 204,219* log (PC ₂₀)	Predose FEV ₁	2-hr Postdose FEV ₁	Placebo* log (PC ₂₀)
1	21	6.39	149	4.65	4.63	4.48	4.51	4.93	2.98
3	24	4.24	86	3.20	3.64	3.95	3.31	3.17	2.94
4	21	3.24	71	3.22	3.77	3.11	3.46	3.45	2.17
5	26	3.73	82	3.54	3.68	3.05	3.06	3.08	2.80
8	21	4.13	89	3.27	4.22	2.80	3.07	3.24	2.73
9	39	2.94	66	3.05	3.13	3.20	2.86	2.96	2.65
10	26	3.13	69	2.95	3.06	1.44	3.26	3.41	1.56
11	42	2.89	71	3.04	2.87	0.77	3.01	3.04	1.65
12	22	3.38	69	3.35	3.42	3.54	3.12	3.11	2.59
13	19	4.27	86	3.99	4.28	3.84	4.30	4.04	2.92
14	18	3.16	75	2.72	3.26	2.07	2.93	3.22	1.18
15	27	3.49	78	2.95	3.17	4.48	3.27	3.40	2.78
Mean	25.5	3.74	82.5	3.33	3.59	3.06	3.35	3.42	2.41
SEM	2.2	0.27	6.4	0.15	0.16	0.33	0.15	0.16	0.18
Geometric mean						1147.5			258.5

*Interpolated PC₂₀.

lunge dose, 0.5, 1, 3, and 5 hours after peak bronchoprovocation response, and before discharge. FVC and FEV₁ were obtained from the full expiratory flow-volume curve.

Statistical analysis

Twelve subjects were included in the study to provide sufficient numbers to determine a statistical difference at a power equal to 95% with an $\alpha < 0.05$. Regression analysis was performed to determine group differences in the rate of change in percent decreases in FEV₁. This analysis included responses at log concentrations of 1 to 3 (10 to 1000 AU/ml). Points selected for this analysis were based on the number of subjects ($N \geq 5$) at a concentration and the trend observed in the mean percent decrease in FEV₁.

When FEV₁ dropped $>20\%$, the PC₂₀ at end point was calculated with log interpolation of the last two data points. Rather than extrapolating beyond these data, the maximum allergen concentration was used to calculate the PC₂₀ for any subject who tolerated the maximum concentration without a 20% decrease in FEV₁. Analysis of variance of a two-period crossover design was used to analyze the allergen dose (Σ concentration times volume) that produced a 20% reduction in FEV₁ (log), quantitative skin test data, vital signs, and laboratory data, and direct effect of ICI 204,219 on pulmonary function. Changes in laboratory data were assessed by Student's paired *t* tests. Pearson's correlation was used to assess the relationship between plasma drug concentrations and the allergen dose needed to produce an effect.

RESULTS

Thirteen of 15 subjects completed the study. One subject was removed from the study after failing a

urine drug screen, and another subject withdrew after a spontaneous asthma attack. Both subjects were removed from the study before receiving ICI 204,219. Twelve of 13 subjects who completed the study had data suitable for challenge-test comparisons. One subject who received placebo developed moderate clinical symptoms during bronchoprovocation. Although the drop in FEV₁ was not $\geq 20\%$, the subject did not complete the provocation procedure. Bronchoprovocation data were incomplete and therefore not used; however, the subject's skin test data were used for evaluation. Demographic characteristics for all subjects are listed in Table I.

ICI 204,219 had no effect on pulmonary function, as is reflected by the lack of change in FEV₁ ($100\% \pm 1\%$) or FVC 2 hours after drug administration.

Skin tests, with allergen and histamine, did not reveal any significant changes between ICI 204,219 and placebo. Eleven of 13 subjects had comparable end point responses to intradermal cat-dander antigen after administration of ICI 204,219 and placebo, whereas two subjects responded to the next higher dose of antigen after treatment with ICI 204,219 ($p > 0.10$). The histamine skin test challenge produced similar results, with nine of 13 subjects responding to the same histamine dose after administration of ICI 204,219 and placebo. Four subjects responded to one or two higher doses of histamine after administration of ICI 204,219.

A significant antagonism of bronchoconstriction oc-

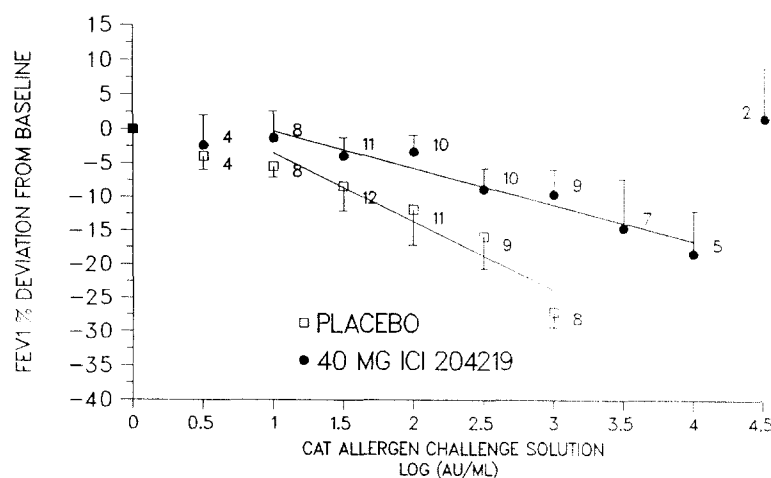


FIG. 1. Rate of change in FEV₁ ($\pm$ SE) percent deviation from baseline until discharge for ICI 204,219 ($\bullet$) and placebo ($\square$). Number varies from five to 13, depending on number of subjects challenged at dose. Point at 30,000 AU ($N = 2$) is illustrated for completeness but was not used to calculate slope.

occurred in subjects receiving ICI 204,219, with a mean shift of 0.57 units in the log dose of allergen (end point allergen units) required to provoke a response. A mean tenfold increase in the interpolated PC₂₀ was observed between ICI 204,219 (6996 ± 3204 AU/ml) and placebo (460 ± 98 AU/ml) (Table II). Eight of 12 subjects required higher antigen concentrations (threefold to 30-fold) to provoke a bronchoprovocation response after treatment with ICI 204,219, three subjects demonstrated no difference between treatments (less than twofold), and one subject required less antigen (sevenfold less).

Regression models, run on the percent change in FEV₁ data, revealed that the best linear fit occurred when data for all allergen doses >3 AU/ml were included. This model excluded 5 of 130 data points at 1 AU/ml. After the linear regression model was fit to data for challenges at allergen doses ≥ 3 AU/ml, a significant difference ($p < 0.01$) was noted in the rate of change of FEV₁ (percent change/log [allergy units per milliliter] after administration of ICI 204,219 (-5.4) and placebo (-10.1) (Fig. 1).

End point and interpolated PD₂₀ were also assessed (Table II). A significant shift ($p < 0.05$) was noted between ICI 204,219 and placebo treatment in the total dose of cat antigen administered to produce a PD₂₀ (1346 ± 537 and 117.4 ± 20.6 AU, respectively). This relationship was retained when the last two points were used to interpolate PD₂₀. The PD₂₀ was 1183 ± 546 AU for subjects treated with ICI 204,219 and 76.1 ± 16.3 AU for subjects treated with placebo ($p < 0.05$).

The change in FEV₁, as a function of time, was assessed from the postdiluent baseline FEV₁ to discharge (Fig. 1). Area under the curve was compared between placebo-treatment and active medication-

TABLE II. Subjects' response to bronchoprovocation ($N = 12$)

Cat dander causing decrease in FEV ₁ $\geq 20\%$	Treatment*	
	ICI 204,219 (two 20 mg tablets)	Placebo (two tablets)
Concentration (AU/ml)		
End point†	8195 $\pm$ 3155	711 $\pm$ 125
Log end point	3.24 $\pm$ 0.32	2.66 $\pm$ 0.16
Interpolation to PC ₂₀	6996 $\pm$ 3204	460 $\pm$ 98
Log PC ₂₀	3.06 $\pm$ 0.33	2.41 $\pm$ 0.18
Cumulative dose (AU)		
End point‡	1346 $\pm$ 537	117.4 $\pm$ 20.6
Log end point	2.45 $\pm$ 0.32	1.88 $\pm$ 0.16
Interpolation PD ₂₀	1183 $\pm$ 546	76.1 $\pm$ 16.3

Statistical analysis performed on log dose; $p < 0.05$ between treatments.

*Data are presented as mean $\pm$ SEM.

†Concentration yielding $\geq 20\%$ (PC₂₀) reduction in FEV₁.

‡Cumulative dose yielding $\geq 20\%$ (PD₂₀) reduction in FEV₁.

treatment days for the fixed time from the end point of the allergen bronchoprovocation to 5 hours after provocation (Fig. 2). Areas under the curve for percent change in FEV₁ from 0 to 5 hours were significantly different ($p < 0.05$) between administration of ICI 204,219 (-9.7) and placebo (-69.6).

Plasma levels of ICI 204,219 ranged from 113 to 565 ng/ml; however, no correlation existed during the active-treatment period between these levels and the degree of blockade exerted by ICI 204,219.

No clinically important drug-related changes were observed from the results of physical examinations.

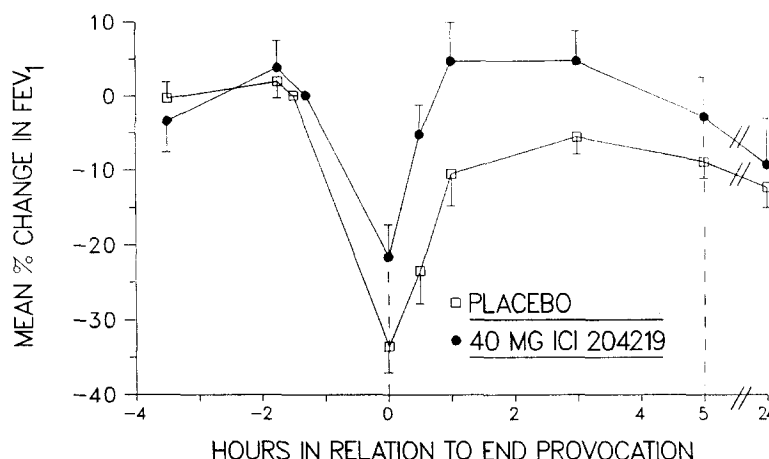


FIG. 2. Measurements of mean change in FEV₁ (N = 12) from end point of bronchoprovocation to 5 hours after provocation for ICI 204,219 (●) and placebo (□).

TABLE III. Adverse experiences

Adverse events (occurrences/subject)	ICI 204,219 (n = 13)	Placebo (n = 15)
Body as a whole		
Asthenia	1/1	1/1
Headache	2/2	4/4
Digestive system		
Dry mouth	2/2	1/1
Liver function abnormality	0	1/1
Nervous system		
Somnolence	2/2	0
Respiratory system		
Asthma	1/1	5/3
Cough	1/1	0
Dyspnea	0	3/1
Laryngismus	0	1/1
Upper respiratory tract infection	1/1	0
Total	10/4	16/9

vital signs, ECGs, pulmonary function tests, or clinical laboratory tests.

Although 60% (9/15) of subjects reported adverse events, none of the events was considered related to treatment. Fewer events were reported by subjects treated with ICI 204,219 (10 events per four subjects) than with placebo (16 events per nine subjects). Headache and asthma occurred with the greatest frequency among subjects in both treatment groups (Table III). The high incidence of headache may be due to caffeine withdrawal.

DISCUSSION

The primary clinical indication for challenges, by both physiologic and pharmacologic methods, is identification of bronchial reactivity.^{11, 12} Inhalation provocation tests are also used to evaluate the efficacy of

antiasthmatic drugs; however, the reproducibility of bronchoprovocation testing in the evaluation of asthma therapies and assessment of dose response depends largely on the method of measurement used, its precision and sensitivity, and the reproducibility of the dose-response curve.¹³ In this study, a single oral 40 mg dose of ICI 204,219 effectively antagonized inhaled antigen-induced bronchoconstriction in subjects with asthma. Administration of ICI 204,219 caused a considerable shift (0.57 units) in the antigen concentration required to induce bronchospasm in this group of subjects. Both the PC₂₀ and PD₂₀ of subjects treated with ICI 204,219 increased compared with that of subjects treated with placebo. Individual effects ranged from increased sensitivity after a single dose of ICI 204,219 (small left shift) to a ≥ 100 -fold protection from cat dander.

It should also be noted that administration of ICI 204,219 did not shift the baseline pulmonary function of subjects undergoing antigen bronchoprovocation. This finding may be due to the baseline status of the subjects in this study. These subjects did not have active asthma symptoms and were normal at the time of provocation. In another study with the 40 mg dose of ICI 204,219, subjects with bronchoconstriction had a modest reversal of airway obstruction.¹⁴

It was hypothesized that without prior blockade of histamine, ICI 204,219 would not have a demonstrable effect on antigen skin testing, since histamine alone can produce an immediate allergic reaction. In each case, as previously demonstrated by Bernstein et al.,¹⁵ histamine-challenge end points were the same (within two dilutions of each other) after treatment with ICI 204,219 and placebo. These data demonstrate that ICI 204,219 had no effect on dermal challenges with cat dander and histamine, confirming the lack of H₁ antagonism of ICI 204,219 in humans. A histamine bronchial challenge was not performed because the

effect of an antigen challenge on subsequent PC₂₀ to histamine would have confounded interpretation of the results with respect to specificity.¹⁶ In extensive pre-clinical pharmacology testing, ICI 204,219 was specific in blocking peptidoleukotriene receptors.¹⁷

ICI 204,219 and other compounds that act on mediators derived from the lipoxygenase pathway have been tested and found effective in attenuating bronchoconstriction induced by allergen and exercise.^{9, 18-21} ICI 204,219 significantly reduced early and late-phase bronchoconstriction to inhaled allergen in a trial of 10 atopic subjects.¹⁸ MK-571 was effective in blocking exercise-induced bronchospasm, with individual protection ranging from <30% to complete inhibition.⁹ However, a correlation between drug effect and plasma concentrations was not demonstrated in this study because MK-571 was administered intravenously to provide a specific blood level. Oral administration of LY171883 produced a significant reduction in the early response to antigen in atopic subjects.¹⁹ In a study of L-649,923 in subjects with mild asthma, a 1000 mg dose produced a modest inhibitory effect on immediate antigen-induced bronchoconstriction.²⁰ A64077, a 5-lipoxygenase inhibitor, ameliorated cold-air-induced bronchoconstriction in subjects with asthma.²¹

These studies, taken together, suggest that drugs of this class will probably be modest bronchodilators but potent inhibitors of environmentally induced bronchoconstriction. The magnitude and distribution of protection suggests that leukotrienes are important mediators of early and late asthmatic responses in most patients. However, clinical experience in asthma efficacy trials reinforces that bronchial challenges are an imperfect predictor of efficacy in the population with asthma.^{22, 23}

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