

Antiallergic activity of loratadine, a non-sedating antihistamine

W. KREUTNER, R. W. CHAPMAN, A. GULBENKIAN and M. I. SIEGEL

Department of Allergy and Inflammation, Schering-Plough Research, Bloomfield, U.S.A.

Loratadine is a new non-sedating antihistamine. The present studies compared loratadine and terfenadine, another non-sedating antihistamine, for their ability to inhibit the bronchial response to histamine and other autacoids which have been implicated as contributing to the symptoms of an allergic reaction. In addition, the two antihistamines were evaluated in models of immunologically mediated allergic reactions. Loratadine is a more potent inhibitor of histamine-induced bronchospasm in guinea pigs than is terfenadine. Both antihistamines exhibit marked antiserotonin activity at doses 10 times their antihistamine ED_{50} values. In contrast, loratadine and terfenadine produce little or no inhibition of the bronchial responses to methacholine, leukotriene C_4 or platelet-activating factor. An allergic bronchospasm in guinea pigs is inhibited by loratadine ($ED_{50} = 0.40$ mg/kg, p.o.) and terfenadine ($ED_{50} = 1.7$ mg/kg, p.o.). The bronchospasm associated with allergic anaphylaxis in rats is significantly inhibited by 10 mg/kg, p.o. loratadine and 30 mg/kg, p.o. terfenadine. Loratadine exhibits antiallergy activity *in vitro*. At micromolar concentrations, loratadine inhibits the release of histamine from Con A and A23187-stimulated rat peritoneal mast cells and the release of histamine and leukotriene C_4 from a Con A-stimulated cloned murine mast cell line

Key words: antiallergic; antihistamine; bronchial spasm; loratadine; mast cell degranulation.

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CLINICAL ASPECTS

Loratadine is a new non-sedating antihistamine that has shown promising activity in clinical trials. In the present study, loratadine is shown to be a selective antagonist of responses to histamine, including allergic pulmonary reactions. In this regard, loratadine is more potent than terfenadine. Loratadine also inhibits mast cell degranulation.

Loratadine, ethyl-4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta(1,2-b) pyridin-11-ylidene)-1-piperidinecarboxylate, is a new non-sedating antihistamine. Previous studies (2) have shown that loratadine exhibits antihistamine activity in guinea pigs and mice with a potency comparable to most standard antihistamines, including the non-sedating antihistamines terfenadine and astemizole.

The studies described in this paper compare loratadine and terfenadine for their ability to inhibit the bronchospastic response to histamine and other autacoids which have been implicated

as contributing to the symptoms of an allergic reaction. In addition, these studies are the first to demonstrate that loratadine is active in models of antigen-induced allergic reactions.

MATERIAL AND METHODS

Spasmogen-induced bronchospasm in guinea pigs

Male Hartley guinea pigs (450-550 g) were obtained from Charles River Breeding Laboratories. The animals were fasted overnight and the

following day were anesthetized with 0.9 ml/kg i.p. of dialurethane (containing 0.1 g/ml diallylbarbituric acid, 0.4 g/ml ethylurea and 0.4 g/ml urethane). The left jugular vein was cannulated for the administration of the spasmogens. The trachea was cannulated and the animals were ventilated by a rodent respirator at 50 strokes/min with a stroke volume of 5 ml. A side arm to the tracheal cannula was connected to a pressure transducer to obtain a continuous measure of inflation pressure. Bronchoconstriction was measured as the percent increase in inflation pressure that occurred within 5 min after challenge with spasmogen. The animals were challenged i.v. with either histamine (10 µg/kg), methacholine (10 µg/kg), 5-hydroxytryptamine (10 µg/kg), PAF (0.5 µg/kg in isotonic saline containing 0.25 % BSA) or LTC₄ (2 µg/kg). Animals that received LTC₄ were pretreated i.v. (15 min) with 1 mg/kg propranolol and 2 mg/kg indomethacin to enhance the direct bronchoconstrictor effect of LTC₄ (18). Each animal was challenged with only a single spasmogen.

Allergic bronchospasm in guinea pigs

Animals were sensitized to ovalbumin and 3–4 weeks later were prepared for the induction of an allergic bronchospasm as described previously (12). Bronchoconstriction was measured as the peak increase in inflation pressure that occurred within 15 min after antigen challenge.

Anaphylactic bronchospasm in rats

Male abino rats (250–300 g) were sensitized to ovalbumin and 2–3 weeks later were surgically prepared for the measurement of lung resistance (R_L) and dynamic lung compliance ($C_{D_{\text{dyn}}}$) as described by Chapman et al. (8). The animals were challenged i.v. with 5 mg/kg ovalbumin dissolved in 0.1 ml of isotonic saline. Bronchoconstriction was recorded as the peak response that occurred within 5 min after antigen challenge.

Histamine release from rat peritoneal mast cells

Male rats (CD-strain, 150 g) obtained from Charles River Breeding Laboratories were

asphyxiated with CO₂. The peritoneal cavity was opened and lavaged with 10 ml of HEPES buffer (25 mM HEPES; 125 mM NaCl; 2.5 mM KCl; 0.7 mM MgCl₂; 1 mM CaCl₂; 10 mM glucose; pH 7.4) which also contained 1 % gelatin and 0.05 % heparin. The lavage fluid was centrifuged for 10 min at 150 *g* at 4°C. The cell pellet of each rat was gently resuspended in 5 ml of HEPES buffer. One-milliliter of cell suspension was incubated with test compound or DMSO vehicle (1 % final concentration) for 5 min at 37°C. The cells were challenged with a final concentration of either 4.5 µg/ml concanavalin A (Con A) or 0.3 µM ionophore A23187. Phosphatidylserine (30 µg/ml) was added to the cells 3 min before they were challenged with Con A. After incubation for 10 min, the reaction was stopped by the addition of 0.6 ml of cold HEPES buffer. The samples were centrifuged (150 *g* for 10 min) and both released histamine and histamine remaining in the cells were determined on perchloric acid-treated samples using a fluorometric method (20) adapted for the Technicon autoanalyzer. Percent inhibition of histamine release was calculated by comparing for each preparation of peritoneal cells the release in the presence to that in the absence of test compound.

Histamine and leukotriene release from MC9 cells

MC9 cells were grown in suspension culture as described by Musch et al. (14). The cells were harvested for assay by centrifugation (150 *g* × 10 min) and washed twice in HEPES buffer (which contained 1 mM CaCl₂). MC9 cells were resuspended at a density of 1 × 10⁶ cells/ml of HEPES buffer and incubated with test compound or DMSO vehicle for 2 min at 37°C. Phosphatidylserine (30 µg/ml) was then added and 3 min later the cells were challenged with 4.5 µg/ml Con A. After incubation for 10 min, the reaction was stopped by the addition of 0.6 ml of cold HEPES buffer. The samples were centrifuged and both released histamine and cellular histamine were determined as described for rat peritoneal cells. A separate 0.3 ml aliquot of supernatant fluid was extracted with 4 volumes of 100 % ethanol. The clear

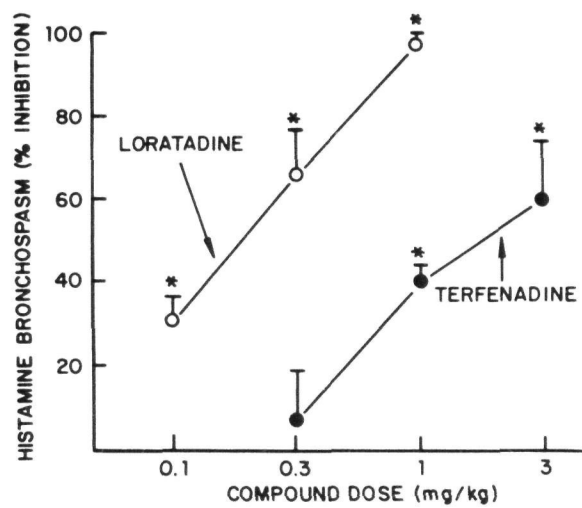


Fig. 1. Inhibition of the bronchospasm to histamine by loratadine and terfenadine. Compounds were administered p.o. 2 h before the challenge with histamine. Symbols indicate the mean $\pm$ SEM percent inhibition of the histamine-induced bronchospasm ($n = 4-8$ per group). * $P < 0.05$ compared to placebo.

fluid was dried under a stream of N_2 gas. The content of leukotriene C_4 (LTC_4) was measured by a radioimmunoassay with [^3H] LTC_4 and antiserum obtained from New England Nuclear.

Calcium uptake by MC9 cells

MC9 cells were suspended at a density of 1×10^6 cells/ml of HEPES buffer which contained 1 mM $CaCl_2$ and 3 μCi $^{45}CaCl_2$ (specific activity

16 mCi/mg; New England Nuclear; Boston, MA). The cells were incubated with test compound or DMSO vehicle for 2 min at $37^\circ C$. Then, phosphatidylserine (30 $\mu g/ml$) was added and 3 min later the cells were challenged with 4.5 $\mu g/ml$ Con A. $^{45}Ca^{2+}$ uptake was stopped after 3 min by the addition of cold HEPES buffer. The cell suspension was centrifuged ($150 g \times 5$ min at $4^\circ C$) and the pelleted cells were washed twice with cold HEPES buffer. The cells were resuspended in 0.5 ml HEPES buffer and filtered by suction on Gelman A/E filters (16). The filters were placed in scintillation vials with Econofluor which contained 0.5 % Protosol for the measurement of radioactivity. Percent inhibition of $^{45}Ca^{2+}$ uptake was calculated by comparing for each preparation of cells the uptake in the presence to that in the absence of test compound.

Material

Loratadine and terfenadine were prepared by the Medicinal Chemistry Department of the Schering-Plough Coporation. LTC_4 was obtained from Professor E. J. Corey (Harvard University). PAF (1-0-alkyl-2-0-acetyl phosphatidylcholine) was obtained from Calbiochem. Histamine diHCl, methacholine Cl, serotonin (5-hydroxytryptamine creatinine sulfate), dl-propranolol HCl, indomethacin, ovalbumin, ionophore A23187 and Con A (con-

Table 1

Effects of antihistamines on the bronchospasms to methacholine, serotonin, LTC_4 and PAF in guinea pigs

Compound ^a	Dose (mg/kg)	Percent inhibition of bronchospasm ^b			
		Methacholine	Serotonin	LTC_4	PAF
Loratadine	0.3	NT	5 $\pm$ 27	NT	NT
	1	24 $\pm$ 10	42 $\pm$ 11 ^c	NT	15 $\pm$ 13
	3	23 $\pm$ 23	53 $\pm$ 7 ^c	NT	29 $\pm$ 11
	10	46 $\pm$ 12 ^c	98 $\pm$ 2 ^c	16 $\pm$ 19	33 $\pm$ 6 ^c
Terfenadine	10	NT	3 $\pm$ 19	NT	15 $\pm$ 13
	30	9 $\pm$ 11	70 $\pm$ 8 ^c	0	57 $\pm$ 9 ^c

^aCompounds were administered p.o. 2 h before the challenge with agonist.

^bMean $\pm$ SEM percent inhibition of the bronchospasm to methacholine, serotonin, LTC_4 or PAF ($n = 3-7$ per group

^c $P < 0.05$ compared to placebo

NT = Not tested

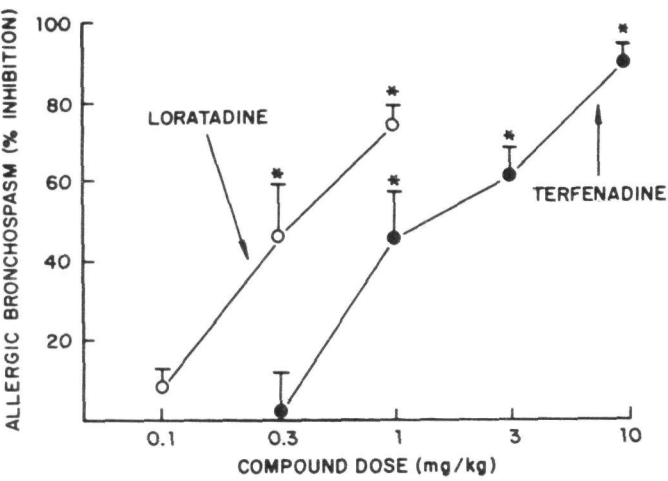


Fig. 2. Inhibition of allergic bronchospasm in guinea pigs by loratadine and terfenadine. Compounds were administered p.o. 2 h before challenge with ovalbumin. Symbols indicate the mean ± SEM percent inhibition of the bronchospasm (*n* = 4–7 per group). **P* < 0.05 compared to placebo.

canavalin A, type IV) were obtained from commercial sources. The doses of all compounds available as salts are expressed as that of the free base.

For *in vitro* experiments, stock solutions of loratadine were prepared in DMSO and then diluted with the appropriate physiological buffer to the final desired concentration. Control samples contained DMSO. For *in vivo* experiments, loratadine or terfenadine were homoge-

nized in methylcellulose vehicle and given orally 2 h before the appropriate challenge.

Statistical analysis

For *in vivo* experiments, statistically significant (*P* < 0.05) differences between treatments were determined by Student’s t-test or analysis of variance using Dunnett’s t-statistic (27). For *in vitro* experiments statistically significant differences were determined using a t-test for paired comparisons.

RESULTS

Spasmogen-induced bronchospasm in guinea pigs

As illustrated in Fig. 1, loratadine (*ED*₅₀ = 0.19 mg/kg, p.o.) was a more potent inhibitor of histamine-induced bronchospasm than was terfenadine (*ED*₅₀ = 1.8 mg/kg, p.o.).

The effect of the antihistamines on the bronchial responses to additional autacoids are summarized in Table 1. Both compounds exhibited antiserotonin activity with loratadine (*ED*₅₀ = 1.8 mg/kg) being more potent than terfenadine (*ED*₅₀ = 20 mg/kg). Loratadine significantly inhibited the response to methacholine only at a dose of 10 mg/kg, while terfenadine was inactive at the highest tested dose. The bronchospasm caused by PAF was

Table 2

Effect of loratadine and terfenadine on anaphylactic bronchospasm in rats

Compound ^a	Dose (mg/kg)	Percent inhibition of bronchospasm ^b	
		R _L	C _{Dyn}
Loratadine	0.1	4±18	0
	1	29±18	22±14
	10	73± 7 ^c	52± 8 ^c
Terfenadine	10	0	0
	30	83± 5 ^c	70±10 ^c

^aCompounds were administered p.o. 2 h before the challenge with ovalbumin
^bMean ± SEM percent inhibition of the changes in R_L and C_{Dyn} due to antigen challenge (*n* = 5–8 per group).
^c*P* < 0.05 compared to placebo.

Table 3

Inhibition of histamine release from rat peritoneal mast cells by loratadine

Compound ^a	Concentration (uM)	Percent inhibition of histamine release ^b	
		Con A	A23187
Loratadine	3	17± 6 ^c	12±10
	10	28± 6 ^c	38±13 ^c
	30	87± 4 ^c	76± 5 ^c

^aLoratadine was added to isolated peritoneal cells 5 min before the addition of Con A or A23187. Con A and A23187 each released 35–40 % of total cell histamine.
^bMean ± SEM percent inhibition of the release of histamine caused by Con A or A23187 (*n* = 6–8 per group).
^c*P* < 0.05 compared to placebo

significantly inhibited only at a high dose of each antihistamine. Neither of the antihistamines antagonized the effects of LTC₄.

Allergic bronchospasm in guinea pigs

Loratadine and terfenadine inhibited an allergic bronchospasm in sensitized guinea pigs provoked by inhalation of specific antigen (Fig. 2). Loratadine (ED₅₀ = 0.40 mg/kg) was more potent than terfenadine (ED₅₀ = 1.7 mg/kg).

Anaphylactic bronchospasm in rats

In rats, allergic anaphylaxis caused a bronchospasm as measured by an increase in lung resistance (R_L) and decrease in dynamic lung compliance (C_{Dyn}). The changes in R_L and C_{Dyn} after antigen challenge were significantly inhibited by loratadine (ED₅₀ = 2.7 mg/kg for R_L and 8.5 mg/kg for C_{Dyn}), and by 30 mg/kg terfenadine. Terfenadine was inactive at 10 mg/kg.

Histamine release from rat peritoneal mast cells

As shown in Table 3, histamine release from Con A-stimulated rat peritoneal mast cells was inhibited in a concentration-dependent manner by loratadine (IC₅₀ = 12 µM). Histamine release induced by ionophore A23187 was also inhibited by loratadine (IC₅₀ = 13 µM). High-

er concentrations (100 µM) of loratadine caused the release of histamine from unchallenged peritoneal cells.

Histamine and leukotriene release and ⁴⁵Ca²⁺-uptake by MC9 cells

MC9 cells stimulated with 4.5 µg/ml Con A released 96 ng LTC₄/10⁶ cells and 24 % of cellular histamine (Table 4). The release of LTC₄ and histamine were inhibited by loratadine (IC₅₀ = 8 µM for LTC₄ and 11 µM for histamine). The enhanced uptake of ⁴⁵Ca²⁺ by MC9 cells stimulated with Con A was significantly inhibited by loratadine (IC₅₀ = 3 µM) at concentrations similar to those that inhibited histamine and LTC₄ release from these cells (Table 4).

DISCUSSION

Loratadine exhibits a similar *in vivo* profile to terfenadine, another non-sedating antihistamine, in experimental models which measure anti-allergy activity. The main distinction is the greater antihistamine potency of loratadine compared to terfenadine. The potencies of loratadine and terfenadine for inhibition of histamine-induced bronchospasm are similar to the potencies of these compounds reported for inhibition of histamine-induced lethality (2) and histamine-induced cutaneous wheal (22) in guinea pigs.

Table 4
Effect of loratadine on the release of LTC₄ and histamine and the uptake of calcium by MC9 cells

Compound ^a	Concentration (uM)	Percent inhibition		
		Release of		⁴⁵ Ca ²⁺ uptake
		LTC ₄	Histamine	
Loratadine	1	NT	NT	24± 8 ^c
	3	22±13	18± 6 ^c	50±10 ^c
	10	50±14 ^c	37±17 ^c	78± 3 ^c
	30	90± 8 ^c	82±10 ^c	91± 3 ^c

^aLoratadine was added to MC9 cells 5 min before the addition of Con A. Con A released 24 % of total cell histamine and 96 ng of LTC₄/10⁶ cells.
^bMean ± SEM percent inhibition of release of LTC₄ or histamine and the uptake of ⁴⁵Ca²⁺ (n = 3-5 per group)
^cP < 0.05 compared to placebo.
NT = Not tested

Loratadine inhibits an allergic bronchospasm in guinea pigs. It is four times more potent than terfenadine. Because histamine released from mast cells is the major mediator of bronchial anaphylaxis in guinea pigs (5, 11, 26), the greater antihistamine potency of loratadine probably accounts for its greater potency in this model of allergic bronchospasm in guinea pigs. The relative potencies of loratadine and terfenadine against an allergic bronchospasm in guinea pigs are in general agreement with the clinically effective dose of 10 mg loratadine (21) and 60 mg terfenadine (4, 22) for seasonal allergic rhinitis.

PAF is a phospholipid which is released from variety of cells (3, 6, 13) and is a potent mediator of systemic anaphylactoid reactions, including bronchospasm, in animals (10, 15, 23). Loratadine and terfenadine produce a small, but significant inhibition of the bronchial response to injected PAF in guinea pigs. These data are consistent with the finding that acute inflammatory responses induced by PAF in guinea pig and human skin are slightly inhibited by H_1 -antihistamines (1).

At doses somewhat higher than their antihistamine ED_{50} values, loratadine and terfenadine exhibit marked antiserotonin activity on guinea pig airways. These data contrast with a previous report (22), that terfenadine possesses little activity against serotonin-induced cutaneous reactions in rats. However, the cutaneous response to serotonin may be indirect due to the release of substance P and therefore not sensitive to blockade by all compounds with antiserotonin activity (17). The antiserotonin activity of loratadine and terfenadine probably contributes to the antianaphylactic effects of these compounds in rats, a species in which serotonin is the predominant mediator of bronchial anaphylaxis (7, 9, 24).

Loratadine, at 50-times its antihistamine ED_{50} , exhibits peripheral anticholinergic activity on the guinea pig airways. However, high doses of loratadine do not antagonize a centrally-mediated physostigmine-induced lethality (2), suggesting that loratadine does not appreciably enter the CNS.

Loratadine exhibits antiallergy activity *in vitro*

in two different mast cell preparations. The rat peritoneal mast cell exhibits the properties of a connective tissue mast cell (19) and the MC9 cell resembles a mucosal mast cell (14). At micromolar concentrations, loratadine inhibits the release of histamine from Con A and ionophore A23187-stimulated rat peritoneal mast cells and the release of histamine and LTC_4 from Con A-stimulated MC9 cells. With either Con A or ionophore A23187, calcium influx is essential for optimal mast cell activation leading to the release mediators (25). Loratadine inhibits Con A-provoked uptake of $^{45}Ca^{2+}$ by MC9 cells at concentrations that also inhibit mediator release from these cells. The effect of loratadine on mediator release and $^{45}Ca^{2+}$ uptake occur at concentrations which are higher than the concentrations of loratadine ($pA_2 = 7.3$) that block contractile responses to histamine on guinea pig ileum (data not shown). However, the concentrations of loratadine that inhibit mediator release are similar to or lower than the concentrations of disodium cromoglycate, theophylline and doxantrazole that inhibit mediator release from rat peritoneal mast cells (25).

In summary, loratadine is more potent than terfenadine in experimental models where histamine is a predominant mediator. This may be of particular clinical importance in the treatment of rhinitis, allergic conjunctivitis and histamine-related dermatological disorders, but less so in allergic asthma. Furthermore, the inhibition of mediator release by loratadine may provide an additional action which contributes to its therapeutic effectiveness.

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Address

Dr. William Kreutner

Department of Allergy and Inflammation

Schering Corporation

60 Orange Street

Bloomfield, New Jersey 07003

U.S.A.

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