Drug Development Research 17:199–206 (1989)

Pharmacologic Modulation by Cetirizine 2 HCl and Loratadine of the Histamine-Induced Skin Reaction in Mice and in Humans

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ABSTRACT

Coulie, P., C. De Vos, L. Ghys, and J.P. Rihoux: Pharmacologic modulation by cetirizine 2 HCl and loratadine of the histamine-induced skin reaction in mice and in humans. Drug Dev. Res. **17**:199–206, 1989.

In mice, the histamine-induced cutaneous reaction is inhibited by cetirizine with an approached ED_{50} of 0.04 mg/kg and by loratadine with an approached ED_{50} of 0.38 mg/kg, both drugs administered intraperitoneally. At these doses, cetirizine's onset of activity seems to be more rapid, although both compounds show the same duration for at least 7 hr. Nine healthy volunteers received orally either cetirizine or loratadine (10 mg single dose) or placebo in a double-blind randomized and cross-over study design. Both drugs were significantly more effective than placebo (except loratadine at the 2nd and 24th hr for the wheal with 1 and 10 μg histamine, and at the 2nd hr for the flare with 1 μg histamine). At all times and with both agonists' concentrations, cetirizine was significantly more potent than loratadine (except at the 24th hr for the wheal with 1 μg histamine). Neither numerous nor marked side effects were found.

Key words: antihistamines, flares, wheals

INTRODUCTION

Several new antihistamines have recently been proposed for the treatment of allergic rhinitis and urticaria: mequitazine, terfenadine, astemizole, and, more recently, cetirizine and loratadine. A common characteristic of these last two drugs is a highly effective anti-H_1 effect

Received revised version September 22, 1988; accepted November 1, 1988.

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after a single per os administration, with few side effects at the central nervous system level [Nicholson, 1987; Gengo et al., 1987; Bradley and Nicholson, 1987]. Several pharmacological and pharmacoclinical comparative studies on cetirizine and loratadine have been published. On histamine-allergen skin test in four different animal species, cetirizine had a more potent and longer-acting activity than mequitazine, clemastine, terfenadine, astemizole, and hydroxyzine [De Vos et al., 1987]. In humans, cetirizine 10 mg was compared with terfenadine 60 mg and 180 mg in inhibiting the histamine-induced wheal and flare [Rihoux and Dupont, 1987]. In this study, cetirizine 10 mg and terfenadine 180 mg were equipotent. Another study, comparing loratadine 160 mg and chlorpheniramine 4 mg, showed a superiority of loratadine in inhibiting the wheal response [Bathenhorst et al., 1986].

Cetirizine and loratadine had not been compared in the same pharmacoclinical study. Both drugs have only been compared with other drugs, with different study designs and with variable dosages. Since the drugs present very similar pharmacokinetic characteristics (single oral intake, rapid absorption, elimination half-time life from 8 to 11 hr [Hilbert et al., 1987; Wood et al., 1987], we have compared them in the same study design and at the clinically advocated doses, to examine a possible difference of potency. Two studies were designed; the first study was conducted in mice and a second in humans, as described.

MATERIALS AND METHODS

Mice

Chemicals. The following drugs were used: cetirizine 2 HCl ([2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride) (UCB, S.A., Belgium), and loratadine (ethyl-4-(8-chloro-5,6-dihydro-11H-benzo [5,6] cyclohepta [1,2,b] pyridin-11-ylidene)-1-piperidine carboxylate) (Schering, U.S.A.). The drugs were dissolved in distilled water containing 9 g/liter NaCl and the pH was then brought back to 7.0 ± 0.2. Histamine 2 HCl (solution concentrations were expressed as histamine-free base) and Evans blue were obtained from Fluka, Switzerland.

Histamine-induced cutaneous reactions in the mouse. An intraperitoneal dose of the test substance was administered to female NMRI mice (UCB breeding unit) aged 6–8 weeks. At different times, the cutaneous reaction was induced by an intradermal injection of a solution of histamine (100 μg/ml histamine base in saline) on the shaved backs of the animals (10 μl/site of injection), followed immediately by a 6 mg intravenous dose of Evans blue (50 mg/ml in saline). The animals were sacrificed 30 min after the induction of the reaction. The two perpendicular diameters were measured; the surface area of the cutaneous blue spots was calculated by application of ellipse surface formula.

Evaluation of drug efficacy. In this experimental scheme there was a control group (receiving vehicle), and at least three groups treated with increasing doses of the drug. The data are expressed as means ± SD. For statistical analysis, Student's *t* test was used for comparison of arithmetic means.

Humans

The protocol (PDIE87L191) was approved by the Ethical Committee of the Braine L'Alleud-Waterloo Hospital. The study design was double-blind, cross-over, and randomized.

Volunteers. Nine healthy volunteers, six women and three men (mean age ± SD: 43.7 ± 10.3 years; mean weight ± SD: 68.2 ± 10.1 kg), duly informed about the drugs used and the experimental conditions, gave their written consent to participate in the study. Up to 1 month before the study, they did not take any anti-H_1 antihistamines nor corticosteroids, nor did they participate in any other clinical trials. During the study no volunteer took medications other than those required for the test.

Drugs. The investigator personally administered in a single oral dosis to fasting

TABLE 1. Cutaneous Reaction to Histamine in Mice (Intraperitoneal administration of the test product 1 hr before intradermal injection of 1 μg histamine in 10 μl saline)†

Product	Dose μmol/kg	Dose = mg/kg	No. of animals	Wheal area (mm^2 ± SD)	% Change of wheal area	Approached ED_{50} μmol/kg	Approached ED_{50} mg/kg
Cetirizine	0	0	8	40 ± 13			
	0.032	0.014	8	29 ± 9 NS	−28		
	0.1	0.046	7	17 ± 5***	−56	0.1	0.046
	0.32	0.147	8	9 ± 3***	−76		
	1.0	0.461	8	5 ± 2***	−87		
Loratadine	0	0	10	62 ± 20			
	0.32	0.127	10	44 ± 12*	−29		
	1.0	0.382	10	28 ± 6***	−55	1.0	0.382
	3.2	1.27	10	25 ± 7***	−60		
	10.0	3.82	10	15 ± 8***	−76		

†Statistical significance (unpaired *t* test). NS, not significant.
*$P < 0.05$.
*** $P < 0.001$.

volunteers loratadine 10 mg (Claritine, Essex-Schering Corporation), cetirizine 10 mg (Zyrtec, UCB S.A.), or placebo in identical and undistinguishable gelatine capsules, with 150 ml of water to ensure good bioavailability at about 8 a.m. The interval between drug administrations was 1 week.

Histamine-induced skin reaction. Cutaneous reactions were induced into the volar surface of the forearms of the volunteers by successive intradermal injections of 10 μl saline, 1 μg histamine in 10 μl saline, and 10 μg histamine in 10 μl saline. The injections were always given by the same investigator throughout the study. For each volunteer a different 10 μl Hamilton syringe was used, and each volunteer was injected with the same syringe. The cutaneous reactivity to saline and histamine was measured before drug intake (time 0) and 2, 4, 6, 8, and 24 hr after drug intake.

Measurement of reactions. Ten minutes after injection the wheal and flare were underlined and reported on a transparent sheet. From this sheet, the objective measurement of the wheal areas was read using a digitizing tablet, as described earlier [Rihoux and Dupont, 1987]. Each wheal area was measured three times. The final value was the mean of these three values, provided the coefficient of variation was lower than 5%. The measures were expressed in square millimeters.

Evaluation of side effects. All volunteers were asked to report any unusual sensation experienced.

Statistical analysis. A three-way analysis of variance (crossed-mixed model) was achieved. The analyzed responses are the evaluations from time zero.

RESULTS

Mice

Administered by intraperitoneal route, cetirizine inhibited the histamine-induced cutaneous reaction (approached ED_{50} = 0.04 mg/kg) (Table 1). Loratadine, under the same circumstances, was less potent than cetirizine (approached ED_{50} = 0.38 mg/kg). The kinetics of action of both compounds were then studied (Table 2). The dose of each compound was selected from the results of the first set of experiments as the dose giving 50% inhibition of the skin histamine reaction (cetirizine: 0.046 mg/kg = 0.1 μmol/kg; loratadine: 0.382 mg/kg = 1 μmol/kg). Under these conditions the effect of cetirizine was faster than that of loratadine. Half an hour after the administration of the i.p. dose, the cetirizine activity was found to be highly significant, whereas that of loratadine at a dose ten times greater on a molar basis did

TABLE 2. Kinetics of the Cutaneous Reaction to Histamine in Mice as Percent of Change of Wheal Area†

Time between drug administration and wheal measurement (hr)	Cetirizine i.p. (0.1 μmol/kg = 0.046 mg/kg)	Loratadine i.p. (1 μmol/kg = 0.382 mg/kg)
0.5	−48***	−19 NS
1	−87***	−55***
2	−76***	−33**
4	−77***	−51***
5	−80***	−38***
7	−36***	−27**

†Drugs were administered IP at time 0, histamine (1 μg/10 μl) was given intradermally at different time intervals, and wheal area was measured. Number of animals: 7–10 in each group. Statistical significance (unpaired *t* test). NS, not significant.
** $P < 0.01$.
*** $P < 0.001$.

not reach the same level of significance. Both compounds appeared to have a stable effect, which lasted for 7 hours. The activities of both compounds started to decrease at hour 7.

Humans

Cetirizine 10 mg vs. placebo. Cetirizine was significantly more effective than placebo at each experimental time and with both agonists' concentrations. The maximum activity occurred between 4 and 8 hr (see Tables 3 and 4, Figs. 1–4).

Loratadine 10 mg vs. placebo. Loratadine was significantly more effective than placebo except at 2 and 24 hr for the wheal with both agonists concentrations, and at 2 hr for the flare with the low histamine concentration (see Tables 3 and 4, Figs. 1–4).

Cetirizine vs. loratadine. Cetirizine was significantly more effective than loratadine at each experimental time except at 24 hr for the low histamine concentration (see Tables 3 and 4, Figs. 1–4).

Side effects. One volunteer complained of thirst with both active drugs and placebo. With loratadine one headache at night was observed in one volunteer, and burning sensations at the level of the injections around 11 a.m. in two volunteers. With cetirizine one volunteer complained of sedation and of thirst.

DISCUSSION

In this study, we compared in mice and in humans the H_1 blocking effect of cetirizine and loratadine. Skin challenges with intradermal injections of histamine were used for this comparison, since the method is rather easy, reproducible, devoid of danger, and of widespread use [Galant et al., 1973; Harvey and Schocket, 1980; Cook and Shuster, 1980; Gendreau-Reid et al., 1986]. Of course, it means that our results will be of value only for cutaneous territory.

In mice, the potency of cetirizine was almost ten times higher than that of loratadine, and the onset of action was also in favor of cetirizine. In humans, cetirizine proved to be more effective than loratadine on both parameters, i.e., wheal and flare, and at both agonists' concentrations. Onset and duration of activity taken as a whole were also better with cetirizine.

According to these results it may be expected that cetirizine will be a useful drug for the treatment of various skin disorders. Indeed, Juhlin et al. [1987] showed that cetirizine 10 mg p.o. in a single dose significantly inhibits a cold-induced urticaria and an experimental

TABLE 3. Percentage of Change ± SEM for the Wheal and the Flare at Various Times (2, 4, 6, 8, and 24 hr) after p.o. Administration of Loratadine 10 mg, Cetirizine 10 mg, or Placebo (DBCO randomized study in humans)[†]

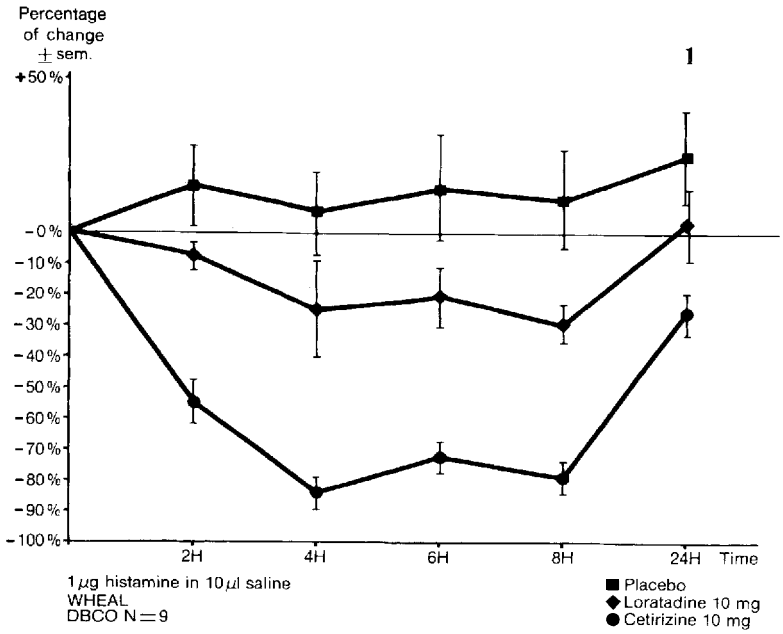
	Time	Cetirizine		Loratadine			
	(hr)	Percent	*P* value[a]	Percent	*P* value[a]	*P* value[b]	Placebo
Wheal[c]	2	−53.3 ± 6.8	***	−6.6 ± 5.6	T	**	+15.4 ± 11.3
	4	−83.6 ± 4.2	***	−24.2 ± 17.6	*	***	+7.0 ± 12.5
	6	−71.9 ± 3.9	***	−20.6 ± 7.8	*	**	+14.6 ± 16.4
	8	−78.9 ± 4.4	***	−29.3 ± 6.1	**	***	+10.6 ± 15.9
	24	−25.1 ± 6.5	**	+3.8 ± 9.4	NS	T	+25.0 ± 16.9
Flare[d]	2	−58.3 ± 14.2	***	+3.5 ± 10.2	NS	***	+21.0 ± 10.1
	4	−82.1 ± 3.9	***	−25.5 ± 9.4	***	***	+37.7 ± 14.9
	6	−90.8 ± 0.9	***	−24.3 ± 14.4	*	***	+12.6 ± 11
	8	−90 ± 1.8	***	−50.8 ± 8.3	***	***	+20.1 ± 14.4
	24	−77.7 ± 4.6	***	−51.1 ± 8.4	**	*	−11.3 ± 13.4

[†]Histamine 1 μg in 10 μl saline s.c. NS, not signficant.
T, $0.05 < P < 0.1$.
$*P < 0.05$., $**P < 0.01$., $***P < 0.001$
[a]Statistical significance vs. placebo.
[b]Statistical significance between cetirizine and loratadine.
[c]Absolute wheal values at time 0 were respectively for cetirizine, loratadine, and placebo: 74.4 ± 3.5, 80.3 ± 4.9, and 89.6 ± 13.4 (mm^2 ± SEM).
[d]Absolute flare values at time 0 were respectively for cetirizine, loratadine, and placebo: 920.9 ± 64.1, 935.8 ± 90.8, and 990.1 ± 138.3 (mm^2 ± SEM).

TABLE 4. Percentage of Change ± SEM for the Wheal and the Flare at Various Times (2, 4, 6, 8, and 24 hr) After p.o. Administration of Loratadine 10 mg, cetirizine 10 mg, or placebo (DBCO randomized study in humans)[†]

	Time	Cetirizine		Loratadine			
	(hr)	Percent	*P* value[a]	Percent	*P* value[a]	*P* value[b]	Placebo
Wheal[c]	2	−55.5 ± 8.0	***	−10.6 ± 7.1	NS	**	+2.2 ± 12.1
	4	−82.8 ± 3.6	***	−16.4 ± 10.4	*	***	+19.7 ± 14.8
	6	−80.2 ± 3.2	***	−13.1 ± 8.0	**	***	+31.7 ± 23.1
	8	−73.7 ± 4.6	***	−35.2 ± 6.4	***	**	+28.1 ± 12.1
	24	−39.1 ± 5.9	***	−0.6 ± 5.9	NS	*	+21 ± 14.4
Flare[d]	2	−47.0 ± 15.6	***	+6.6 ± 11	*	***	+35.4 ± 12.2
	4	−76.6 ± 6.3	***	−14.9 ± 11.9	**	***	+25.1 ± 19.4
	6	−78.4 ± 3.9	***	−19.3 ± 11.7	**	**	+27.7 ± 19.3
	8	−83.7 ± 3.0	***	−37.1 ± 8.9	***	***	+15.5 ± 15.4
	24	−73.3 ± 7.2	***	−33.4 ± 10.2	***	**	+16.6 ± 29.9

[‡]Histamine 10 μg in 10 μl saline s.c. NS, not significant.
T, $0.05 < P < 0.1$, $*P < 0.05$., $**P < 0.01$, $***P < 0.001$.
[a]Statistical significance vs. placebo.
[b]Statistical significance between cetirizine and loratadine.
[c]Absolute wheal values at time 0 were respectively for cetirizine, loratadine, and placebo: 130.6 ± 9.7, 125.0 ± 9.6, and 135.3 ± 16.3 (mm^2 ± SEM).
[d]Absolute flare values at time 0 were respectively for cetirizine, loratadine, and placebo: 1061.7 ± 120.8, 1,106.2 ± 109.5, and 1,167 ± 140.9 (mm^2 ± SEM).


Percentage
of change
± sem.
1
+50%
-0%
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-40%
-50%
-60%
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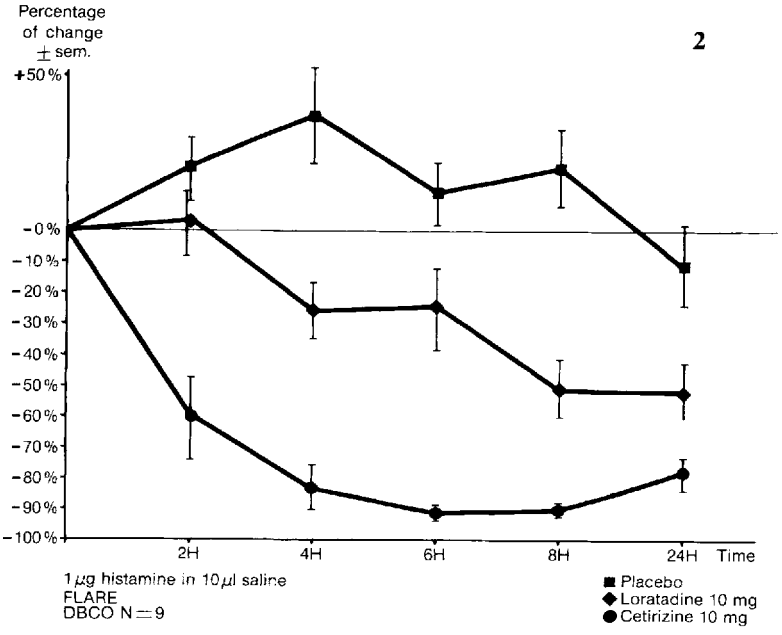
-80%
-90%
-100%
2H
4H
6H
8H
24H
Time
1 μg histamine in 10 μl saline
WHEAL
DBCO N = 9
Placebo
Loratadine 10 mg
Cetirizine 10 mg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2
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2H
4H
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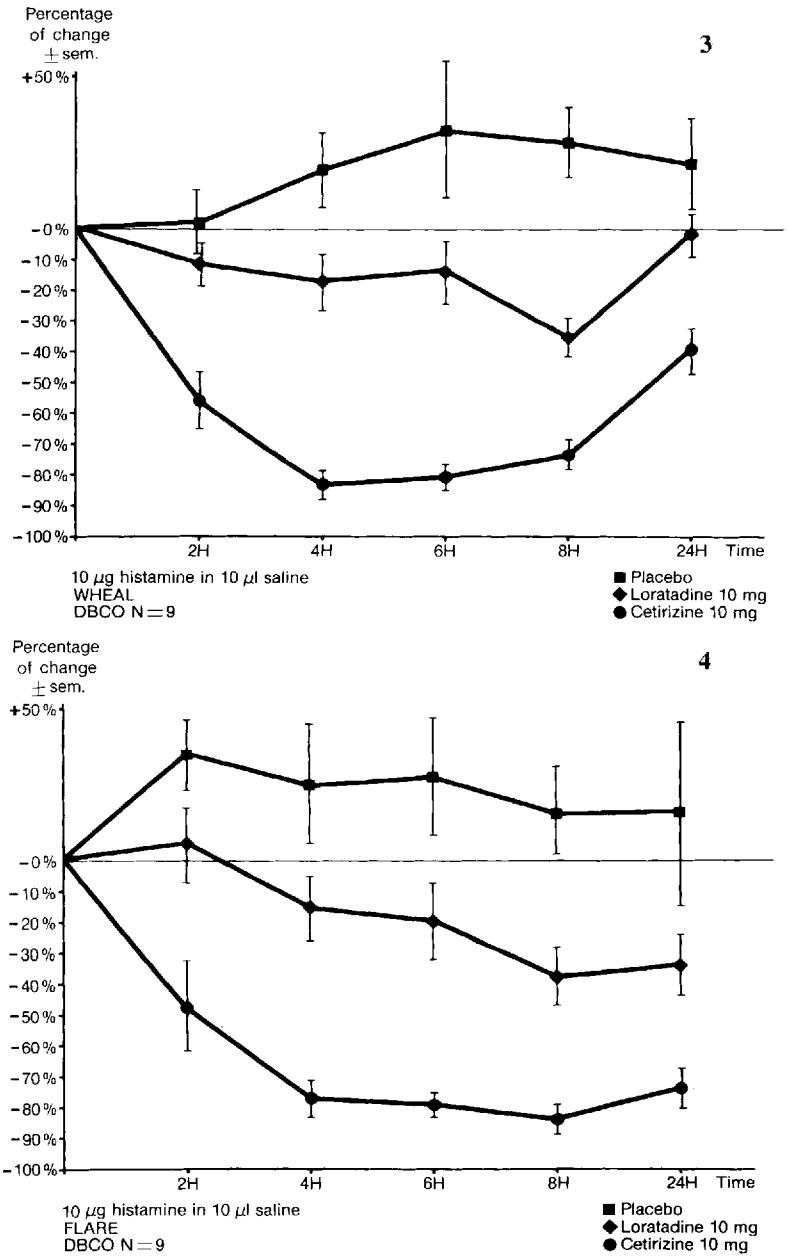
8H
24H
Time
1 μg histamine in 10 μl saline
FLARE
DBCO N = 9
Placebo
Loratadine 10 mg
Cetirizine 10 mg



Figs. 1–4. Percentage of change ± SEM for the wheal and the flare at 0, 2, 4, 6, 8 and 24 hr with 1 and 10 μg histamine in 10 μl saline after p.o. administration of loratadine 10 mg, cetirizine 10 mg or placebo (DBCO randomized study in humans).

dermographism, and Dockx et al. [1987] demonstrated that this drug has good clinical efficacy in patients suffering from chronic idiopathic urticaria.

As far as loratadine is concerned, our results describe a rather weak H_1 blocking effect at a dose of 10 mg, which is recommended once a day for the treatment of rhinitis and urticaria. It is known that loratadine 160 mg in a single dose is significantly more effective in suppressing the skin reactivity to histamine than chlorpheniramine maleate 4 mg (Batenhorst et al., 1986], but this dose is far from the recommended one. In the management of chronic idiopathic urticaria, loratadine 10 mg a day proved to be more effective than placebo [Bernstein and Bernstein, 1988].

We conclude from this cetirizine-loratadine comparison that cetirizine at the advocated dose of 10 mg appears to be more effective than loratadine at the same dose in terms of objective parameters such as histamine-induced wheals and flares. We plan to confirm these first results by a more sophisticated study using three different doses of each drug and different histamine concentrations, keeping in mind that only the clinical studies will give us in the long run the right answer about this drug comparison.

ACKNOWLEDGMENTS

We thank Pierre Dupont for statistical analysis.

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