

Clinical pharmacology of H₁-antihistamines in the skin

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Background: The extent of the distribution of H₁-antihistamines into the skin and H₁-antihistamine activity in the skin are clinically relevant in the treatment of allergic skin disorders.

Methods: In a prospective, randomized, double-blind, parallel-group, multiple-dose study, we gave fexofenadine 180 mg, loratadine 10 mg, or chlorpheniramine 8 mg to 21 men (7 in each group). Before dosing and at 1, 3, 6, 9, and 24 hours after the first antihistamine dose as well as at 168, 192, and 216 hours after the first dose (ie, 12, 36, and 60 hours after the seventh and last consecutive daily H₁-antihistamine dose), we measured fexofenadine, loratadine, or chlorpheniramine concentrations in plasma and in skin tissue samples obtained through use of punch biopsies, along with suppression of histamine-induced skin wheals and flares. Loratadine metabolites, including desloratadine and its metabolites, were not measured, and chlorpheniramine metabolites were not measured.

Results: All 21 participants completed the study. Skin/plasma fexofenadine ratios ranged from 1.2 ± 0.5 at 1 hour to 110 ± 74 at 24 hours, and skin fexofenadine concentrations exceeded loratadine and chlorpheniramine skin concentrations at each test time. This was reflected in significant wheal and flare suppression by fexofenadine in comparison with loratadine at 3 hours and in comparison with chlorpheniramine at 6 and 9 hours (wheal) and from 3 to 24 hours and at 192 hours (flare). Compared with fexofenadine, loratadine significantly suppressed the wheal at 192 hours, and compared with chlorpheniramine, it significantly suppressed the wheal at 9 hours and the flare at 24 and 192 hours. At no time did chlorpheniramine suppress the wheal or flare significantly more than fexofenadine or loratadine.

Conclusions: In skin disorders for which H₁-antihistamines are recommended, these results support the use of fexofenadine or loratadine, and they indicate the need for reexamination of the use of chlorpheniramine. (*J Allergy Clin Immunol* 2002;110:777-83.)

Key words: Histamine, H₁-antihistamine, fexofenadine, loratadine, chlorpheniramine, skin punch biopsy, wheal, flare, antihistaminic activity, adults, urticaria

Clinical pharmacology studies help us to understand why some H₁-antihistamines, despite high potency in preclinical investigations, are relatively ineffective in the treatment of allergic disorders.¹⁻³ There are few randomized, double-blind, comparative clinical pharmacology studies of H₁-antihistamines—this despite the fact that some of these medications have been used in the treatment of allergic skin disorders for 60 years.³⁻⁵ Measurements of H₁-antihistamine concentrations in plasma and skin and correlation of these concentrations with peripheral H₁-antihistamine activity are helpful in determining similarities and differences among H₁-antihistamines with regard to onset, extent, and duration of activity and in developing optimal recommendations for dosing. Moreover, skin H₁-antihistamine concentrations correlate with cutaneous H₁-antihistamine activity.^{6,7}

The nonsedating H₁-antihistamines fexofenadine and loratadine and the sedating H₁-antihistamine chlorpheniramine are among the medications most commonly used by ambulatory patients in the United States.⁸ These H₁-antihistamines have terminal elimination half-life values of 14, 8, and 24 hours, respectively.^{1,2} Fexofenadine is eliminated largely unchanged in the feces. Loratadine is metabolized to descarboethoxyloratadine (desloratadine), which is itself further metabolized. Chlorpheniramine is metabolized to desmethyl chlorpheniramine, didesmethylchlorpheniramine, and other metabolites.

We hypothesized that fexofenadine and loratadine would penetrate the skin as well as or better than chlorpheniramine and would have equal or greater peripheral H₁-antihistamine activity. In a prospective, randomized, double-blind, parallel-group, multiple-dose study of these 3 medications, we measured skin and plasma H₁-antihistamine concentrations and the relative onset, extent, and duration of their H₁-activity as evidenced by wheal and flare suppression.

METHODS

Participants

Healthy young men with no histories of skin disease were recruited. During a preliminary visit to the Allergy Research Laboratory, each was interviewed and given an opportunity to discuss the test procedures. Prospective participants were excluded if they were obese or prone to scar formation or if their skin precluded accurate visualization and tracing of the histamine-induced flare response. They were also excluded if they had histories of smoking, illicit drug use, excessive alcohol ingestion, or adverse reaction to H₁-antihistamines or if they needed to use any medication.

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The study protocol was approved by the University of Manitoba Research Ethics Board. Each participant gave written, informed consent before enrollment.

Study design

On the first study day, participants arrived at the laboratory at approximately 8:00 AM, having fasted for 8 hours. Baseline skin punch biopsy, venipuncture, and histamine skin tests were performed. The techniques used for these procedures are described subsequently. Each participant was then randomly allocated to receive one of the following: fexofenadine 180 mg (3×60 mg Allegra tablets, Aventis Pharma Inc, Laval, Quebec, Canada); loratadine 10 mg (Claritin tablet, Schering Canada Inc, Pointe Claire, Quebec, Canada); or chlorpheniramine 8 mg (2×4 mg Chlor-Tripolon tablets, Schering Canada Inc).⁹ The H₁-antihistamines were dispensed and ingested at 9:00 AM in opaque, sealed capsules to ensure double-blinding. The biopsies, venipunctures, and skin tests were repeated in the same sequence at 1, 3, 6, 9, and 24 hours after H₁-antihistamine administration. Each participant received a standardized breakfast consisting of fruit juice and a muffin 2 hours after H₁-antihistamine administration and a standardized lunch and dinner 4 and 8 hours, respectively, after H₁-antihistamine administration.

At 9:00 PM on day 2, 36 hours after receiving the first H₁-antihistamine dose, each of the participants took a second dose of the same H₁-antihistamine; this dose was repeated at 9:00 PM on each of the next 5 days. Skin punch biopsies, venipunctures, and histamine skin tests were repeated at 168, 192, and 216 hours after the first dose—ie, 12, 36, and 60 hours after the seventh and last consecutive H₁-antihistamine dose. Each participant logged in by voice mail at the precise time that he took his daily H₁-antihistamine dose. Compliance was also confirmed by capsule count at the end of the study and by the H₁-antihistamine measurements in skin and plasma.

Skin biopsies and venipunctures

The skin biopsies were performed on the medial surfaces of the thighs with a 3-mm AccuPunch device (Acuderm, Fort Lauderdale, Fla) 15 minutes after infiltration of the biopsy site with 1% lidocaine, 0.01 mg/mL epinephrine, and 0.1 mEq/mL sodium bicarbonate. A different site was used for each biopsy, and the sequence of sites was the same in each participant. The sites were sutured. Polymyxin B sulfate/bacitracin ointment (Polytopic, Technilab Pharma Inc, Mirabel, Quebec, Canada) was applied.

All biopsy samples were blotted free of blood through use of surgical gauze, transferred to nonabsorbent paper, and stored in a sealed polypropylene tube at -20°C until analysis for fexofenadine, loratadine, or chlorpheniramine was performed.

Seven-milliliter blood samples were obtained by venipuncture and centrifuged at 4°C . Plasma was transferred into appropriately labeled polypropylene tubes, sealed, frozen promptly in the upright position, and stored at -20°C until analysis for fexofenadine, loratadine, or chlorpheniramine was performed.

Measurement of fexofenadine, loratadine, and chlorpheniramine in skin and plasma samples

Skin and plasma samples were randomly coded in such a way that the individuals measuring the fexofenadine, loratadine, or chlorpheniramine concentrations were blinded to the participant and to the sample time. Fexofenadine and loratadine concentrations were measured at Quintiles (Kansas City, Mo); chlorpheniramine concentrations were measured in our laboratory.

Before analysis of H₁-antihistamine concentrations in the skin, tissue samples were weighed by means of an analytical balance, thawed, and placed in 250 μL of 2 mol/L potassium hydroxide for

24 to 60 hours until the skin was found on inspection to be completely digested.

Fexofenadine skin and plasma concentrations were measured at Quintiles through use of HPLC tandem mass spectrometry, as described in our previous study.⁷ The limit of quantification of fexofenadine was 0.5 ng. Loratadine skin and plasma concentrations were also measured at Quintiles through use of a modified HPLC tandem mass spectrometry assay.¹⁰ The limit of quantification of loratadine was 0.5 ng. Loratadine metabolites, including desloratadine and its metabolites, were not measured. Chlorpheniramine skin and plasma concentrations were measured in our laboratory through use of an HPLC-UV assay, modified from the method described previously for brompheniramine.¹¹ The limit of quantification of chlorpheniramine was 3 ng. Chlorpheniramine metabolites were not measured.

Skin tests

Epicutaneous tests were performed with histamine phosphate 1 mg/mL (Bioniche Pharma, London, Ontario, Canada) through use of a straight needle and the prick-through drop technique. A different site on the volar surfaces of the forearm was used for each test, and the sequence of test sites was the same in each participant. The wheal and flare circumferences were traced with a pen at 10 minutes and transferred to paper with transparent tape. All skin tests and tracings were performed by the same nurse. All wheal and flare areas were measured from the circumference tracings by the same investigator through use of a digitizer and stereometric measurement software (SigmaScan, Jandel Scientific, San Rafael, Calif) on a personal computer (IBM, Armonk, NY). For the time during which these measurements were performed, the coefficient of variation of reproducibility was 4.5% for areas of 0.2 cm², representative of wheal areas traced, and 0.9% for areas of approximately 4 cm², representative of flare areas traced. The epicutaneous tests were performed in duplicate, and these duplicate results were averaged before statistical analysis.

Data analysis

Skin fexofenadine, loratadine, or chlorpheniramine concentrations were compared within participants receiving the same H₁-antihistamine and between participants receiving fexofenadine, loratadine, or chlorpheniramine over time through use of 2-way ANOVA and the Tukey and Bonferroni multiple range tests. Differences were considered significant at $P \leq .05$. Fexofenadine, loratadine, and chlorpheniramine skin/plasma ratios were calculated and were also compared within medications and between medications over time.

Wheal and flare areas at each time were compared with predose values for fexofenadine, loratadine, or chlorpheniramine through use of 2-way ANOVA and the Tukey and Bonferroni multiple range tests, differences being considered significant at $P \leq .05$. Wheal and flare percent suppression after fexofenadine administration was compared with the suppression after loratadine and chlorpheniramine administration through use of the same statistical tests and level of significance.

Correlations between skin and plasma fexofenadine, loratadine, or chlorpheniramine concentrations and percent suppression of the histamine-induced wheals and flares by fexofenadine, loratadine, and chlorpheniramine were evaluated through use of pharmacodynamic methods.¹² When possible, the skin H₁-antihistamines that were associated with maximum wheal and flare suppression were identified.

RESULTS

Twenty-one men were randomized to receive fexofenadine, loratadine or chlorpheniramine treatment, and all of them completed the study. Seven of the men (age, 26 ± 3 years; weight, 83 ± 6 kg; body-mass index, 25 ± 2) received fexofenadine, 7 (age, 30 ± 3 years; weight, 94

± 6 kg; body-mass index, 29 ± 2) received loratadine, and 7 (age, 25 ± 2 years; weight, 85 ± 6 kg; body-mass index, 25 ± 2) received chlorpheniramine. Despite randomization, the participants in the loratadine group were older and heavier ($P \leq .05$) than those in the fexofenadine and chlorpheniramine groups, which did not differ significantly from each other.

Plots of skin and plasma concentrations versus time for fexofenadine, loratadine, and chlorpheniramine are shown in Fig 1 (A, B, and C, respectively). Mean skin fexofenadine concentrations were higher than mean plasma fexofenadine concentrations at all times after the first fexofenadine dose as well as at steady-state (168, 192, and 216 hours after the first dose—ie, 36, and 60 hours after the seventh and last consecutive dose); they differed significantly at 6, 24, 168, 192, and 216 hours ($P \leq .05$; Fig 1, A). Mean skin/plasma fexofenadine ratios ranged from a minimum of 1.2 ± 0.5 at 1 hour to a maximum of 110 ± 74 at 24 hours.

The H_1 -activity of fexofenadine in skin is shown in Fig 2. After epicutaneous tests with histamine phosphate, fexofenadine produced, in comparison with baseline, significant suppression of the wheals and flares from 3 to 216 hours ($P \leq .05$). Mean maximum wheal suppression ($68\% \pm 6\%$ to $74\% \pm 6\%$) and mean maximum flare suppression ($90\% \pm 3\%$ to $92\% \pm 2\%$) occurred at 3, 6, 9, and 168 hours.

Skin and plasma loratadine concentrations are shown in Fig 1, B. Although plasma loratadine concentrations were consistent with previously reported values,² only a limited number of skin and plasma concentrations were quantifiable because of a combination of small tissue samples and very low H_1 -antihistamine concentrations; concurrent skin and plasma data in the same participants at the same times were scarce. Skin/plasma concentration ratios were 9 and 58, respectively, 1 and 3 hours after the initial dose.

The H_1 -activity of loratadine in skin is shown in Fig 2. After epicutaneous tests with histamine phosphate, loratadine produced, in comparison with baseline, significant wheal suppression from 6 to 216 hours and flare suppression from 9 to 216 hours ($P \leq .05$). Mean maximum wheal suppression of $66\% \pm 6\%$ occurred at 9 hours after the first dose; mean maximum wheal suppression of $68\% \pm 5\%$ to $70\% \pm 5\%$ occurred at 168 and 192 hours—ie, 12 and 36 hours after the seventh consecutive dose. Mean maximum flare suppression of $81\% \pm 9\%$ occurred at 9 hours after the first dose; mean maximum flare suppression of $78\% \pm 11\%$ to $82\% \pm 9\%$ occurred at 168, 192, and 216 hours—ie, 12, 36, and 60 hours after the seventh consecutive dose.

Plots of skin and plasma chlorpheniramine concentration versus time are shown in Fig 1, C. Mean skin chlorpheniramine concentrations were higher than plasma chlorpheniramine concentrations at 1 hour and from 6 to 24 hours (inclusive) after the first chlorpheniramine dose as well as at 168, 192, and 216 hours—ie, 12, 36, and 60 hours after the seventh and last consecutive dose. Mean skin/plasma chlorpheniramine ratios ranged from a minimum of 11 ± 2 at 6 hours to a maximum of 49 ± 2 at 192 hours.

The H_1 -activity of chlorpheniramine in skin is shown in Fig 2. After epicutaneous tests with histamine phosphate, chlorpheniramine produced, in comparison with baseline, significant wheal suppression from 3 to 192 hours and significant flare suppression at 9 and 168 hours ($P \leq .05$). Mean maximum wheal suppression of $46\% \pm 11\%$ occurred at 3 hours after the first dose; mean maximum wheal suppression of $51\% \pm 9\%$ occurred at 168 hours—ie, 12 hours after the seventh and last consecutive dose. Mean maximum flare suppression of $58\% \pm 10\%$ occurred at 9 hours after the first dose; mean maximum flare suppression of $71\% \pm 10\%$ occurred at 168 hours—ie, 12 hours after the seventh consecutive dose.

At 3, 6, 9, 24, and 168 hours, the mean skin fexofenadine concentrations were in the 400-600 ng/g range—considerably higher than mean chlorpheniramine skin concentrations, which were in the 80-135 ng/g range. At 24 hours, the skin/plasma ratios for fexofenadine were significantly higher than the skin/plasma ratios for chlorpheniramine ($P \leq .05$).

Fexofenadine significantly suppressed the wheal and flare at 3 hours in comparison with loratadine and significantly suppressed the wheal at 6 and 9 hours and the flare at 3, 6, 9, 24 and 192 hours in comparison with chlorpheniramine. Loratadine suppressed the wheal significantly more than fexofenadine at 192 hours and significantly suppressed the wheal at 9 hours and the flare at 24 and 192 hours in comparison with chlorpheniramine. Chlorpheniramine did not produce significantly greater wheal or flare suppression than fexofenadine or loratadine at any time.

Pharmacodynamic analysis through use of the $E_{\max}$ (maximum pharmacologic activity achievable) model¹² yielded “loops of hysteresis” that precluded the determination of a reliable EC_{50} value (plasma concentration that achieves 50% of $E_{\max}$) for fexofenadine or chlorpheniramine; however, fexofenadine skin concentrations of 600 ng/g resulted in 74% and 92% histamine-induced wheal suppression and flare suppression, respectively. Chlorpheniramine skin concentrations of 70 ng/g yielded 58% and 71% histamine-induced wheal suppression and flare suppression, respectively. There were an insufficient number of quantifiable loratadine skin concentrations to permit correlation with wheal and flare suppression.

DISCUSSION

Claims for H_1 -antihistamine potency, based on preclinical in vitro studies and in vivo studies in animal models, often appear to bear little relationship to the efficacy of H_1 -antihistamines documented in clinical trials in chronic urticaria and other disorders. The main reason for this is that some antihistamines, because of their pharmacokinetic properties in humans, are not absorbed into plasma or distributed into tissue as well as others.

Here we have explored the relative distribution into the skin of the second-generation H_1 -antihistamines fexofenadine and loratadine versus the first-generation H_1 -antihistamine chlorpheniramine. We have found that on a

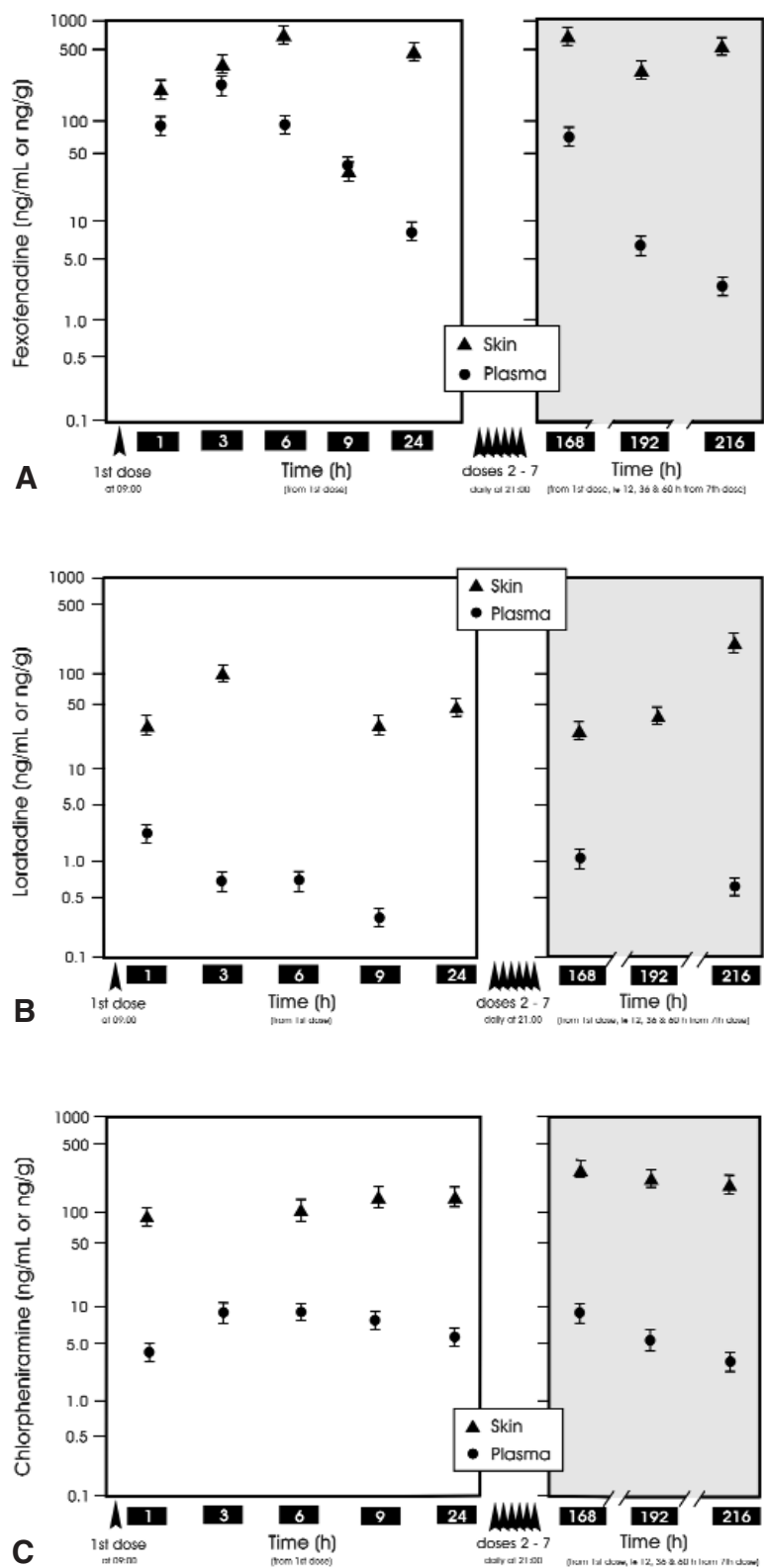


FIG 1. Plots of skin and plasma concentrations versus time for fexofenadine 180 mg (**A**), loratadine 10 mg (**B**), and chlorpheniramine 8 mg (**C**). Arrows indicate days and times of dosing; shaded areas indicate measurements made at steady-state after the seventh and last dose. Some data points are missing because of lack of quantifiable values (small tissue samples/very low H_1 -antihistamine concentrations) in participants at these test times.

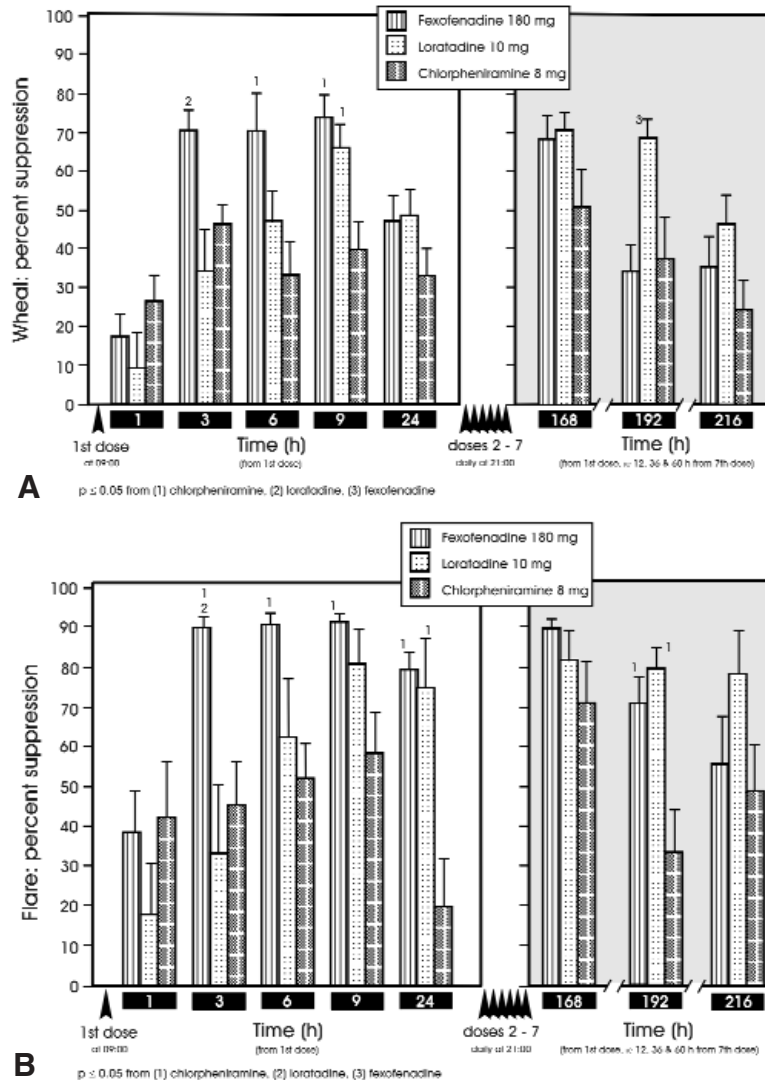


FIG 2. Wheal suppression (%) versus baseline (**A**) and flare suppression (%) versus baseline (**B**), calculated from wheal and flare areas after epicutaneous tests with 1 mg/mL histamine phosphate. Arrows indicate days and times of H₁-antihistamine dosing; shaded areas indicate measurements made at steady-state after the seventh and last dose.

molar basis, fexofenadine showed a 10-fold greater distribution into the skin than either loratadine or chlorpheniramine. Skin and plasma fexofenadine concentrations found in this study were slightly but not significantly higher than those noted in our previous study, in which the dose of fexofenadine was 120 mg once daily.⁷

Both fexofenadine and loratadine were superior to chlorpheniramine in terms of peripheral H₁-activity. Fexofenadine produced significant wheal and flare suppression by 3 hours and appeared to have a faster onset of action than loratadine or chlorpheniramine. Moreover, its maximum effect on wheal and flare suppression occurred 3 to 9 hours after the first dose; in contrast, the maximum effects of loratadine and chlorpheniramine appeared at steady-state after 7 consecutive H₁-antihistamine doses. The offset of action of the H₁-antihistamines was not yet complete when the last skin tests were performed, 2.5 days

after the last H₁-antihistamine dose, at which time mean flare suppression was approximately 80% for loratadine, 60% for fexofenadine, and 50% for chlorpheniramine.

Fexofenadine has no active metabolites that might contribute to wheal and flare suppression. Loratadine, which has a terminal elimination half-life value of 8 hours after a 10-mg dose, is rapidly metabolized in the hepatic cytochrome P450 system to descarboethoxy-loratadine (desloratadine), which has a terminal elimination half-life of 21 to 31 hours after a 7.5-mg dose and is itself metabolized. Desloratadine skin concentrations were not determined in this study because of limitations in the amount of tissue that could be obtained in the 9 sequential skin biopsies performed in each participant. In this and other clinical pharmacology studies, the amount of wheal and flare suppression produced after loratadine administration by the parent compound loratadine versus

the amount produced by the major active metabolite desloratadine and other metabolites has not been determined.² Similarly, the active metabolites of chlorpheniramine were not measured, and their contribution to the wheal and flare suppression produced by chlorpheniramine has not been determined.

The evidence base supporting the use of H₁-antihistamines in allergic skin disorders is relatively weak in comparison with the evidence base for their use in allergic rhinoconjunctivitis. In chronic urticaria treatment, the evidence base supporting the use of fexofenadine is stronger than that for any other H₁-antihistamine; it consists of 3 large prospective, randomized, double-blind, placebo-controlled trials of 4 to 6 weeks' duration involving more than 1000 patients.¹³⁻¹⁵ The evidence base for the efficacy of loratadine in urticaria consists of several smaller, randomized, placebo-controlled, double-blind trials.¹⁶⁻¹⁸ Although chlorpheniramine use in chronic urticaria is based on more than 5 decades of anecdotal experience, the evidence base supporting its use in this disorder is surprisingly small.¹⁹

The efficacy of H₁-antihistamines in skin disorders such as urticaria is attributed primarily to their H₁-antihistaminic activity on small unmyelinated afferent C-fibers to reduce itching, on neurogenic reflexes to reduce erythema (flares), and on the epithelial cells of the postcapillary venules to reduce leakage of fluid and cells and resultant wheals.^{20,21} H₁-antihistamines also downregulate inflammatory cell accumulation through H₁-receptor-dependent anti-inflammatory effects on adhesion protein expression.²²

The present study was not designed to permit assessment of the relative daytime sedation produced by fexofenadine 180 mg, loratadine 10 mg, and chlorpheniramine 8 mg. After the initial H₁-antihistamine dose, which was given in the morning, daytime sedation could not be assessed reliably because of the invasiveness of the study—in particular, because of participants' anxieties about the skin biopsies. The subsequent 6 H₁-antihistamine doses were given in the evening to avoid potential daytime sedation from chlorpheniramine and loss of double-blinding. In considering the relative benefits and risks of these 3 H₁-antihistamines, however, it is important to note that fexofenadine 180 mg and loratadine 10 mg, which had significantly greater peripheral H₁-activity than chlorpheniramine, have not been reported to cause sedation or psychomotor impairment.²³ Indeed, even in a dose of 360 mg, fexofenadine does not cross the blood-brain barrier to any extent (as assessed directly through use of positron emission tomography).²⁴ In contrast, the 8-mg dose of chlorpheniramine, which had significantly less peripheral H₁-activity than fexofenadine or loratadine, was 4 times larger than the 2-mg dose of chlorpheniramine that has been demonstrated to cross the blood-brain barrier, saturate more than 80% of the H₁-receptors in the central nervous system, and impair central nervous system function.^{23,25,26}

In summary, clinical pharmacology studies such as this one, in which pharmacokinetic/pharmacodynamic rela-

tionships are expressed as plasma and skin concentrations versus effect over time, help us to understand why some H₁-antihistamines that are potent in preclinical studies appear to be less efficacious than others in humans.

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