

Skin concentrations of H₁-receptor antagonists

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Background: H₁-receptor antagonists are widely used in the treatment of allergic skin disorders.

Objective: We sought to evaluate the extent of fexofenadine and diphenhydramine distribution into the skin concomitantly with their peripheral H₁-receptor antagonist activity.

Methods: In a prospective, randomized, double-blind, parallel-group study, 7 men received 120 mg of fexofenadine, and 7 received 50 mg of diphenhydramine. Before dosing; at 1, 3, 6, 9, and 24 hours after the first dose; and at 168 hours (steady-state), 12 hours after the seventh and last daily dose, blood samples and skin punch biopsy specimens were obtained, and epicutaneous tests with histamine phosphate, 1 mg/mL, were performed.

Results: Fexofenadine penetrated the skin to a significantly greater extent than diphenhydramine at 6, 9, 24, and 168 hours ($P \leq .05$). Maximum skin/plasma ratios of both the H₁-antagonists (41.3 ± 7.8 for fexofenadine and 8.1 ± 4.4 for diphenhydramine) were obtained at 24 hours. Fexofenadine also produced significantly greater suppression of wheals at 3, 6, and 9 hours and of flares at 3, 6, 9, and 168 hours compared with diphenhydramine ($P \leq .05$).

Conclusion: In disorders in which the presence and the effects of H₁-receptor antagonists in the skin are clinically relevant, our results support the use of fexofenadine and indicate the need to re-examine the role of diphenhydramine. (J Allergy Clin Immunol 2001;107:526-30.)

Key words: H₁-receptor antagonist, antihistamine, fexofenadine, diphenhydramine, skin punch biopsy, wheal, flare, histamine blockade, adults, urticaria

H₁-receptor antagonists relieve symptoms in skin disorders in which histamine is the major chemical mediator of inflammation.¹⁻³ They act primarily at H₁-receptors on the postcapillary venules in the skin to prevent histamine-induced vasodilation, increased vascular permeability, and wheal reactions.⁴ They also act through a neurogenic reflex to prevent histamine-induced erythema (flaring)⁴ and act at the H₁-receptors on small, extensively branching, unmyelinated C-fibers in the skin to prevent pruritus.⁵ In addition, many of them have antiallergic and anti-inflammatory activity in the skin.⁶ Measurement of H₁-

Abbreviation used

E_{max}: Maximum effect attributable to drug

antagonist concentrations in plasma and correlation of these concentrations with the peripheral H₁-blockade produced by the H₁-antagonist is helpful in determining onset of action, relative potency, and duration of action and in developing optimal recommendations for dose and dose frequency.⁷ Measurement of H₁-antagonist concentrations in the skin, although seldom performed, may provide a more direct correlation with cutaneous H₁-blockade.⁸

We hypothesized that the nonsedating H₁-antagonist fexofenadine would penetrate the skin as well as or better than the potentially sedating H₁-antagonist diphenhydramine and that skin concentrations of these H₁-antagonists would correlate with the onset, extent, and duration of the H₁-blockade they produce in the skin. We tested this hypothesis in a prospective, randomized, double-blind, parallel-group study.

METHODS

Participants

Healthy young men without skin disease were recruited. Participants were excluded if they were obese, prone to scar formation, or had very dark skin precluding accurate visualization and tracing of the histamine-induced flare response. They were also excluded if they had a history of smoking, recreational drug use, excessive alcohol ingestion, or adverse reaction to H₁-receptor antagonists or if they needed to use any medication.

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

Study design

During a preliminary visit to the allergy research laboratory, the participants were given the opportunity to discuss the test procedures. On the first study day, they arrived at the laboratory at 8 AM after an 8-hour fast. Baseline skin punch biopsy, venipuncture, and histamine skin tests were performed. The patients were then randomly allocated to receive either 120 mg of fexofenadine (2 × 60 mg Allegra tablets; HMR Canada Inc, Laval, Quebec, Canada) or 50 mg of diphenhydramine (Benadryl capsule; Parke-Davis, Scarborough, Ontario, Canada). The H₁-antagonists were dispensed 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-antagonist administration. The techniques used for these procedures are described subsequently.

Participants received a standardized breakfast consisting of fruit juice and a muffin 2 hours after H₁-antagonist administration and a standardized lunch and dinner 4 and 8 hours after H₁-antagonist administration, respectively.

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Beginning 36 hours after receiving their first dose of fexofenadine or diphenhydramine, they took 120 mg of fexofenadine or 50 mg of diphenhydramine (whichever H₁-antagonist they had received on the first study day) at 9 PM for the next 6 consecutive days. Skin punch biopsies, venipunctures, and histamine skin tests were repeated at 168 hours (steady-state), 12 hours after the seventh and last H₁-antagonist dose.

Compliance with the medication regimen was prompted by having the participants log in by using voice mail at the precise time they took each daily H₁-antagonist dose, by means of capsule counts at the end of the study, and by measuring the H₁-antagonist concentrations in skin and plasma.

Skin biopsies and venipunctures

The skin biopsies were performed on the medial surfaces of the thighs with a 3-mm Accu-Punch device (Acuderm, Fort Lauderdale, Fla) 15 minutes after the biopsy site was infiltrated 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. Polymixin B sulfate/bacitracin ointment (Polytopic; Technilab Pharma, Inc, Mirabel, Quebec, Canada) was applied.

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

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

Measurement of fexofenadine and diphenhydramine in skin and plasma samples

Skin and plasma samples were randomly coded so that the individuals measuring fexofenadine and diphenhydramine concentrations were blinded to the participant and to the sample time. Fexofenadine concentrations were measured at Quintiles (Kansas City, Mo). Diphenhydramine concentrations were measured in our laboratory.

Before analysis of H₁-antagonist concentrations in the skin, tissue samples were weighed on an analytic balance, thawed, and placed in 250 μ L of 2 mol/L potassium hydroxide for 24 to 60 hours until, on inspection, the tissue was completely digested.

Fexofenadine. After the addition of 250 μ L of internal standard solution, the skin samples were acidified with 250 μ L of glacial acetic acid and extracted by using 5 mL of methyl-t-butyl ether with vortex mixing for 15 minutes, followed by centrifugation for 10 minutes at 4500 rpm. The methyl-t-butyl ether layer was transferred and evaporated to dryness under vacuum. The dried samples were reconstituted in 20 μ L of acetonitrile and then diluted with a 60- μ L mobile phase. Chromatography was performed on an octadecylsilane column (2 $\times$ 30 mm, 3 μ m) at 40°C by using a gradient system. The mobile phases were as follows: phase A, buffer (10 mmol/L ammonium hydroxide and 87 mmol/L glacial acetic acid, pH 3.5)/acetonitrile 95:5; and phase B, buffer/acetonitrile 5:95. At a flow rate of 0.4 mL/min, the mobile phase was increased from 15% phase B to 95% phase B over 4 minutes and then reduced to 15% phase B by 7.4 minutes. Under these conditions, the internal standard and fexofenadine eluted at 2.6 and 2.8 minutes, respectively. Quantitative detection was performed by using positive electrospray on a Finnigan TSQ-700/SIM mass spectrophotometer. The limit of quantification of the fexofenadine assay was 0.5 ng.⁹

Plasma fexofenadine samples were diluted with acetonitrile after the addition of 250 μ L of internal standard solution and centrifuged. The supernatant was analyzed by using the HPLC-tandem mass

spectroscopy conditions described for the skin samples.

Diphenhydramine. After the addition of 250 μ L of internal standard solution, the skin samples were extracted twice with 5 mL of diethyl ether by using vortex mixing for 10 minutes, centrifugation at 1600g, and an acetone-dry ice bath to enhance phase separation. The ether layers were extracted independently with 100 μ L of 5% phosphoric acid, again using vortex mixing for 10 minutes and centrifugation at 1600g. The acid phases were combined, and 175 μ L was injected into an Alliance Separations Module 2690 HPLC with Millennium 32 software, attached to a 996-photodiode array detector (Waters Corp, Milford, Mass) under the same conditions as described previously.¹⁰

After the addition of 250 μ L of 2 mol/L potassium hydroxide and 250 μ L of internal standard solution, the plasma samples were extracted by using the same conditions as those used for the tissue samples, except that only one 5-mL diethyl ether extraction was required. The limit of quantification of the diphenhydramine assay was 3 ng.¹⁰

Skin tests

Epicutaneous tests were performed with 1 mg/mL histamine phosphate (Bioniche Inc, London, Ontario, Canada) by using a straight needle and the prick-through drop technique.¹¹ A different site on the volar surface 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 tracings by the same investigator using a digitizer and stereometric measurement software (SigmaScan; Jandel Scientific, San Rafael, Calif) on an IBM PC. During the time 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. The epicutaneous tests were performed in duplicate.

Data analysis

Skin fexofenadine or diphenhydramine concentrations were compared within subjects receiving the same H₁-antagonist and between subjects receiving fexofenadine or diphenhydramine, respectively, over time by using 2-way ANOVA and the Tukey and Bonferroni multiple-range tests. Differences were considered significant at *P* values of .05 or less. Fexofenadine and diphenhydramine skin/plasma ratios were calculated and were also compared within medications and between medications.

Wheal and flare areas at each time were compared with predose values for fexofenadine or diphenhydramine by using ANOVA and the Tukey and Bonferroni multiple-range tests, with differences being considered significant at a *P* value of .05 or less. Wheal and flare areas after fexofenadine administration were compared with the areas after diphenhydramine administration by using the same statistical tests and level of significance.¹²

Correlations between skin and plasma fexofenadine concentrations and percentage suppression of the histamine-induced wheals and flares by fexofenadine and diphenhydramine were evaluated by using pharmacodynamic methods. Plots of percentage wheal and flare suppression versus skin and plasma fexofenadine and diphenhydramine concentrations were fitted by using the E_{max} (observed maximum effect attributable to drug) model.^{13,14}

RESULTS

Fourteen men were randomized to either fexofenadine or diphenhydramine treatment, and all completed the study. Seven (age, 27 $\pm$ 3 years; weight, 77 $\pm$ 3 kg)

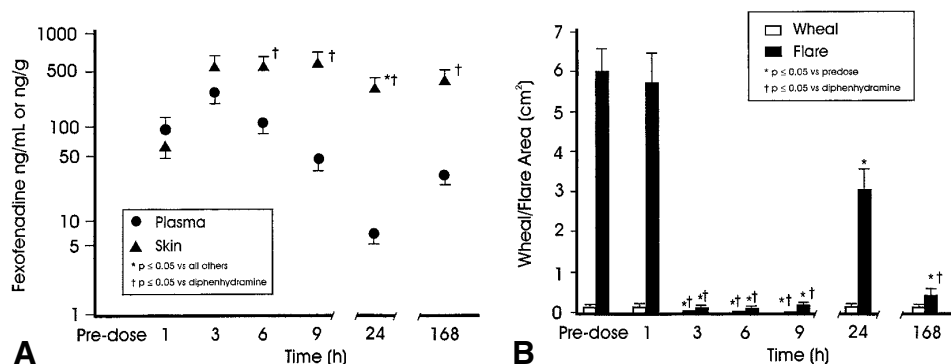


FIG 1. Skin and plasma fexofenadine concentration versus time plots (**A**) and wheal and flare areas after epicutaneous tests with 1 mg/mL histamine phosphate (**B**). Tests were performed at baseline and 1, 3, 6, 9, and 24 hours after the initial dose of 120 mg of fexofenadine. Participants then took 120 mg of fexofenadine at 9 AM for 6 consecutive days, and all tests were repeated at 168 hours (steady-state), exactly 12 hours after the seventh and last fexofenadine dose. Fexofenadine penetrated the skin to a significantly greater extent than diphenhydramine at 6, 9, 24, and 168 hours, as evidenced by significantly higher skin/plasma ratios ($P \leq .05$). It also produced significantly greater suppression of wheal reactions at 3, 6, 9, and 168 hours ($P \leq .05$).

received fexofenadine, and 7 (age, 25 ± 2 years; weight, 77 ± 5 kg) received diphenhydramine.

Skin and plasma fexofenadine concentration versus time plots are shown in Fig 1, A. Skin fexofenadine concentrations were higher than plasma fexofenadine concentrations at 3, 6, 9, and 24 hours after administration of the first fexofenadine dose and at 168 hours (steady-state), 12 hours after the seventh and last dose, but differed significantly only at 24 hours ($P \leq .05$). Skin/plasma fexofenadine ratios ranged from a minimum of 0.9 ± 0.4 at 1 hour to a maximum of 41.3 ± 7.8 at 24 hours. At 168 hours (steady-state), the ratio was 16.4 ± 4.8 .

The H_1 -blockade produced by fexofenadine in skin is shown in Fig 1, B. After epicutaneous tests with histamine phosphate, compared with baseline values, fexofenadine produced significant suppression of the wheals at 3, 6, and 9 hours and of the flares at 3, 6, 9, 24, and 168 hours ($P \leq .05$). Maximum wheal and flare suppression of 96% to 100% occurred at 3, 6, and 9 hours.

Skin and plasma diphenhydramine concentration versus time plots are shown in Fig 2, A. Skin diphenhydramine concentrations were higher than plasma diphenhydramine concentrations at 3, 6, 9, and 24 hours after the initial diphenhydramine dose and at 168 hours (steady-state), 12 hours after the final dose, but did not differ significantly at any time ($P > .05$). Skin/plasma diphenhydramine ratios ranged from a minimum of 1.4 ± 1.4 at 1 hour to a maximum of 8.1 ± 4.4 at 24 hours. At 168 hours (steady-state), the ratio was 1.7 ± 0.9 .

The H_1 -blockade produced by diphenhydramine in skin is shown in Fig 2, B. After epicutaneous tests with histamine phosphate, compared with baseline values, diphenhydramine produced significant wheal suppression at 3 and 6 hours and produced significant flare suppression at 3 hours ($P \leq .05$). Maximum wheal suppression of 32% occurred at 6 hours, and maximum flare suppression of 73% occurred at 3 hours.

At 3, 6, 9, 24, and 168 hours, the mean skin fexofenadine concentrations were in the 400 to 600 ng/g range. This is considerably higher than mean diphenhydramine skin concentrations, which were in the 80 to 90 ng/g range. At 6, 9, 24, and 168 hours, the skin/plasma ratios for fexofenadine were significantly higher than the skin/plasma ratios for diphenhydramine ($P \leq .05$). Fexofenadine produced significantly greater wheal and flare suppression than diphenhydramine at 3, 6, and 9 hours and significantly greater flare suppression at 168 hours ($P \leq .05$). Diphenhydramine did not produce significantly greater wheal or flare suppression than fexofenadine at any time.

DISCUSSION

In this study 120 mg of fexofenadine once daily, a lower dose than the 180-mg once daily dose currently recommended in most countries,¹⁵ penetrated the skin well and suppressed the histamine-induced flares for 24 hours. Maximum histamine blockade occurred from 3 to 9 hours, which is similar to the results of a previous study, in which it occurred from 3 to 12 hours¹¹; no 12-hour test was performed in the present study. In contrast, a single dose of 50 mg of diphenhydramine was not particularly effective in penetrating the skin or in suppressing the histamine-induced wheal and flare reactions. At 3 and 6 hours, the mean diphenhydramine skin concentrations of 2.8×10^{-10} mol/g (83 ng/g) and 2.3×10^{-10} mol/g (68 ng/g), respectively, were lower than the mean fexofenadine skin concentrations of 1.03×10^{-9} mol/g (518 ng/g) and 1.01×10^{-9} mol/g (507 ng/g), respectively.

Although diphenhydramine may appear to have been studied at a disadvantage because it was administered in a dose of 50 mg once daily, this was not so. On a molar basis, the diphenhydramine dose of 50 mg (1.7×10^{-4} mol) was similar to the fexofenadine dose of 120 mg (2.4×10^{-4} mol). The low skin/plasma diphenhydramine con-

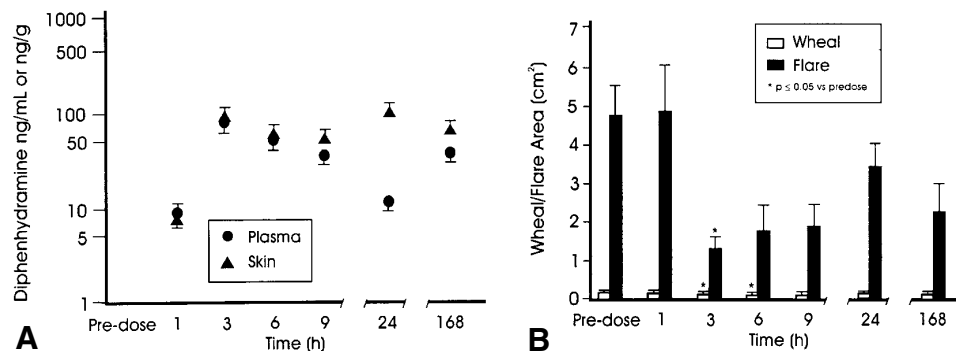


FIG 2. Skin and plasma diphenhydramine concentration versus time plots (**A**) and wheal and flare areas after epicutaneous tests with 1 mg/mL histamine phosphate (**B**). Tests were performed at baseline and 1, 3, 6, 9, and 24 hours after the initial dose of 50 mg of diphenhydramine. Participants then took 50 mg of diphenhydramine at 9 AM for 6 consecutive days, and all tests were repeated at 168 hours (steady-state), exactly 12 hours after the seventh and last diphenhydramine dose. Diphenhydramine neither penetrated the skin nor suppressed the wheal and flare reactions as well as fexofenadine.

centration ratios associated with modest wheal and flare suppression at 3 and 6 hours after the first diphenhydramine dose were found within the recommended 4- to 6-hour dose interval for diphenhydramine.¹⁵

The plasma diphenhydramine concentrations and the modest wheal and flare suppression produced by 50 mg of diphenhydramine in this study were similar to those found in a previous study in which a higher diphenhydramine dose (87.9 ± 12.4 mg) was administered on a milligram per kilogram basis to young adults, and skin diphenhydramine concentrations were not measured. In the earlier study maximum wheal suppression was $45.5\% \pm 25\%$ and maximum flare suppression was $53.4\% \pm 16.9\%$ at 6 and 4 hours, respectively; compared with baseline values, significant wheal suppression occurred only at 10 hours, and significant flare suppression occurred only at 2, 4, and 6 hours.¹⁰

In the present study pharmacodynamic analysis of the plasma fexofenadine and diphenhydramine concentrations using the $E_{\max}$ model yielded the expected loop of hysteresis.¹⁴ Mean skin fexofenadine concentrations above 500 ng/g, which occurred from 3 to 9 hours, correlated with greater than 80% to 90% suppression ($E_{\max}$) of the wheal and flare reaction. Optimally, venipunctures and skin biopsies would have been performed at regular intervals between 9 and 24 hours in order to calculate the skin fexofenadine concentration producing 50% of the $E_{\max}$, but because of the invasive nature of the biopsies, these samples were not obtained. Mean skin diphenhydramine concentrations never exceeded 90 ng/g and correlated with maximum wheal and flare suppressions ($E_{\max}$) of 30% and 70%, respectively.

The design of the study did not permit us to ascertain whether the H_1 -antagonists detected in the skin were located in the extracellular fluid, were bound to H_1 -receptors on cells, or both. Attempts to delineate the concentrations of another H_1 -antagonist, cetirizine, in the skin extracellular water compartment by using a microdialysis technique during a 3-hour study suggest that H_1 -

antagonist concentrations in the dialysate (non-protein-bound H_1 -antagonist fraction only) are extremely low.¹⁶

In addition, the design of the study did not permit us to assess potential daytime sedation associated with H_1 -antagonist administration. Only the first H_1 -antagonist dose was given during the day. Despite reassurance and injection of a local anesthetic before each skin biopsy, most participants experienced some anxiety about this procedure, and this subjective complaint predominated over any sedation they may have also experienced. The 6 subsequent H_1 -antagonist daily doses were given in the evening to avoid potential daytime sedation and loss of double blinding.

Pharmacodynamic studies, such as the one reported here, provide a useful model for comparison of H_1 -receptor antagonist potency, as well as onset and duration of action in the skin. This study facilitates understanding of fexofenadine's prompt onset of action and prolonged duration of action in significantly reducing itching and wheal size, number, and duration in chronic urticaria over a very wide dose range from 60 to 240 mg daily to 20 to 240 mg twice daily.¹⁷⁻¹⁹ The findings also suggest that in allergic skin disorders, fexofenadine, which is actually present in the skin in high concentrations, is likely to be more effective than diphenhydramine, which is present in relatively low concentrations. Currently, both fexofenadine and diphenhydramine are widely used in the treatment of chronic urticaria. The evidence for the efficacy and effectiveness of fexofenadine has been obtained in prospective, randomized, double-blind, placebo-controlled, clinical trials of 4 to 6 weeks' duration in more than 1000 participants.¹⁷⁻¹⁹ In contrast, the evidence for the efficacy and effectiveness of oral diphenhydramine is based on trials in relatively few participants²⁰⁻²²; although these studies were blinded, they were not placebo controlled, and some were only of 5 to 7 days' duration.^{20,22} An adequately powered, prospective, randomized, placebo-controlled, comparative 1-month clinical trial of fexofenadine versus diphenhydramine in chronic urticaria would be of considerable interest.

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