
Suppression of histamine- and allergen-induced skin reactions: comparison of first- and second-generation antihistamines

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Background: Nonsedating antihistamines (nsAHs) are recommended as first-line therapeutics for the treatment of mast cell–driven disorders, including allergic rhinitis and urticaria. However, their superiority over first-generation AHs (fgAHs) has recently been called into question, mainly because of the lack of supporting head-to-head therapeutic studies.

Objective: To compare the effects of 3 modern nsAHs with those of the fgAH hydroxyzine on histamine- and allergen-induced skin reactions in a controlled, double-blind, clinical trial.

Methods: Skin prick tests with histamine and *Dermatophagoides pteronyssinus* extract were performed before and 4 hours after treatment with hydroxyzine, 25 mg; desloratadine, 5 mg; epinastine, 20 mg; fexofenadine, 120 mg; or placebo. Wheal and erythema development was evaluated by digital photography and planimetric analyses.

Results: The nsAHs prevented the development of positive reactions to histamine in only 10% to 20% of all individuals tested ($n = 75$). In contrast, more than 50% of all hydroxyzine-treated individuals showed negative test reactions to histamine (ie, wheals $<7 \text{ mm}^2$ in area or $<3 \text{ mm}$ in diameter). Similar differences, although less pronounced, were detected when comparing the effects of nsAHs with hydroxyzine on *D pteronyssinus* prick testing in a limited number of *D pteronyssinus*–sensitized individuals.

Conclusions: These results indicate that hydroxyzine is more effective than nsAHs when given as recommended in suppressing histamine-induced or allergic skin reactions. Our results suggest that higher doses of nsAHs than those currently recommended are required for the treatment of skin responses to obtain antihistaminic and antiallergic effects that are equivalent to those of fgAHs.

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INTRODUCTION

Antihistamines (AHs) are first-choice drugs in the treatment of allergic disorders, including allergic rhinitis (AR) and other mast cell–mediated diseases such as chronic urticaria or mastocytosis. Current treatment guidelines for these diseases recommend the use of second-generation nonsedating AHs (nsAHs).^{1,2} These recommendations are based on the fact that nsAHs have been shown to be effective and safe in the treatment of AR, chronic urticaria, and mastocytosis.^{3,4} The nsAHs are also to be preferred to older first-generation AHs (fgAHs) because they have less sedative effects.⁵

However, fgAHs are still widely used for the treatment of histamine-driven diseases. This is most likely because of any one or a combination of the following reasons: (1) fgAHs

are usually available without prescription and are cheaper than nsAHs, which are not reimbursed by medical insurance in some countries⁶; (2) patients and physicians are familiar with fgAHs and, therefore, reluctant to switch to novel compounds they are not experienced with using⁷; (3) the safety profiles of fgAHs are well characterized because of their frequent use for more than 4 decades⁸; and (4) fgAHs are frequently considered to exhibit better antihistaminic effects compared with nsAHs. The latter assumption appears to be widely accepted despite contradicting literature.^{9,10,11}

Therefore, we have performed a prospective, randomized, placebo-controlled, double-blind, and parallel-group designed study to compare the efficacy of nsAHs (desloratadine, epinastine, and fexofenadine) with that of the fgAH hydroxyzine in reducing histamine- or allergen-induced wheal-and-flare responses. Our results reveal that nsAHs given at recommended daily doses are less effective than hydroxyzine in suppressing skin reactions to histamine or allergen prick testing in a 4-hour time point analysis.

METHODS

Design

This study was performed as an interventional, double-blind, placebo-controlled, parallel-group clinical trial comparing the

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effects of first- with second-generation AHs on histamine and *Dermatophagoides pteronyssinus*-induced skin reactions. The study protocol was approved by the local research ethics committee, and all participants provided signed informed consent.

Participants

Seventy-five consecutive volunteers (students or employees from Curitiba University Hospital, Curitiba, Brazil) were included in this study (age range, 19–61 years; mean [SD] age, 28.8 [8.9] years; 42 women). None of them had been treated with AHs, mast cell stabilizers, or corticosteroids during the 2 weeks before testing. Individuals receiving immunotherapy or experiencing dermatological diseases at the test area were excluded.

Clinical Trial

The participants were stratified in 5 equal groups (15 volunteers each) and received a single-dose oral treatment (tablet) with hydroxyzine, 25 mg (commercial preparation), an nsAH (fexofenadine, 120 mg; epinastine, 20 mg; or desloratadine, 5 mg [all commercial preparations]), or placebo 4 hours before testing. The AH doses were chosen according to the manufacturers' recommendation and the current guidelines on the treatment of AR and urticaria.¹ The placebo was a white 25-mg tablet containing lactose.

Skin Prick Tests

Skin prick tests with histamine, *D pteronyssinus*, and sterile saline were performed before and 4 hours after AH or placebo treatment, as previously described.¹² Briefly, 1 drop of histamine, 10 mg/mL (IPI-ASAC, São Paulo, Brazil); *D pteronyssinus* extract, 113 kU/mL (IPI-ASAC); and saline solution (IPI-ASAC) were applied on the left forearm anterior surface. Sterile 26-gauge needles were used in all prick tests. Test results were evaluated after 10 minutes by digital photography and planimetric analysis. Test reactions that showed a wheal of 3 mm or more in diameter or 7 mm² or more in area (erythema, ≥ 10 mm in diameter or ≥ 80 mm² in area) were considered positive.^{13,14}

Evaluation of Test Reaction

Images of test reactions were obtained using a digital camera (Olympus 650°C; Olympus Corporation, Tokyo, Japan), and further analyses were performed using Adobe Photoshop 6.0 (Adobe Systems, Inc, San Jose, California), as previously described.¹² Briefly, the image areas that showed wheals or erythema were highlighted by the use of distinct filter masks, and diameters and areas were evaluated using the Adobe Photoshop 6.0 measuring tool. The results are expressed as means (SDs). For planimetric analysis, a ruler was used to measure the longest and the midpoint orthogonal diameter of the wheal and the erythema reaction, and the mean diameter was calculated. All data were analyzed using the Pearson χ^2 test. $P < .05$ was considered to indicate differences of statistical significance.

RESULTS

Suppression of Histamine-Induced Skin Reactions in Most Individuals Treated With Hydroxyzine

Fexofenadine, epinastine, and desloratadine, given at recommended daily doses, prevented positive prick test reactions to histamine¹³ in only 10% to 20% of all 75 individuals tested, as evaluated by digital photography (Fig 1A). In contrast, more than 50% of all hydroxyzine-treated individuals showed negative prick test reactions to histamine. As seen in Figure 1B, virtually identical results were obtained using planimetric analyses to detect positive (ie, ≥ 3 mm in diameter) skin reactions to histamine.

In addition, the rates of responders to AH treatment correlated well with wheal size suppression in the different treatment groups. The maximum suppression was seen in hydroxyzine-treated individuals (75% reduction for histamine and 57% reduction for allergen). All 3 nsAH treatment groups showed less reduction in the size of histamine-induced wheal reactions (ie, 32%, 55%, and 58% suppression in individuals treated with desloratadine, epinastine, and fexofenadine, respectively).

Similar differences, although less pronounced, were detected comparing the erythema size of skin test reactions to histamine in AH-treated individuals (Fig 1C and D). Hydroxyzine treatment prevented the development of positive test reactions in 60% of all individuals tested (Fig 1C). In contrast, nsAH treatment prevented positive erythema reactions in only 8% (desloratadine), 24% (epinastine), and 40% (fexofenadine) of individuals tested. Assessing erythema sizes by digital photography and traditional planimetric analysis yielded essentially equivalent results (Fig 1D).

Suppression of Prick Test Reactions to Allergen in Most Individuals Treated With Daily Recommended Doses of Hydroxyzine

To evaluate whether nsAHs and hydroxyzine are also different in their efficacy to suppress skin reactions induced by allergen, we performed a pilot study and evaluated AH effects on skin prick test reactions to *D pteronyssinus* in sensitized individuals (31 of 75 individuals) treated with placebo, hydroxyzine, or nsAHs as done previously. We found that nsAHs prevented the development of positive wheal and erythema reactions to prick testing in only half or less of all patients treated (Table 1). In contrast, up to 70% of all hydroxyzine-treated individuals showed negative test reaction results to skin prick testing as evaluated by digital photography or planimetric analyses of wheal-and-flare reactions (Table 1).

DISCUSSION

In the present study, the fgAH hydroxyzine was compared with desloratadine, epinastine, and fexofenadine, 3 modern nsAHs. We found that all of the nsAHs were less effective than hydroxyzine in preventing histamine- and allergen-induced wheal-and-flare responses when given at recommended doses. To our knowledge, this is the first study that

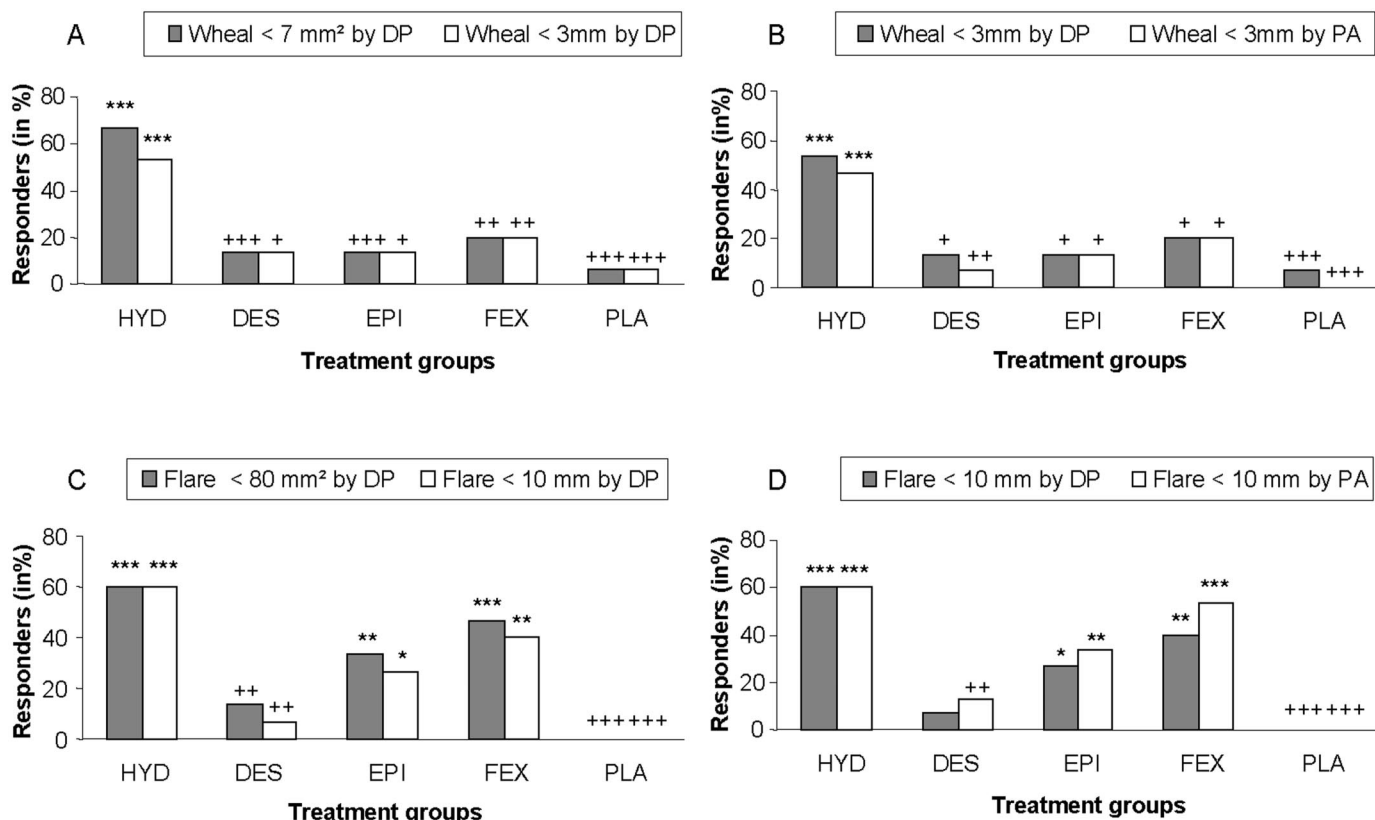


Figure 1. Hydroxyzine (HYD), but not desloratadine (DES), epinastine (EPI), or fexofenadine (FEX), suppresses positive skin reactions to histamine prick testing in most of the individuals treated. A and B, Reduction in positive skin test reactions to histamine prick testing as assessed by measuring wheals (A, digital photography [DP] area and diameter; B, DP and planimetric analysis [PA] diameter). C and D, Reduction in positive reactions to histamine prick testing as assessed by measuring erythema (C, DP area and diameter; D, DP and PA diameter). * $P < .05$ vs placebo, ** $P < .01$ vs placebo, *** $P < .001$ vs placebo, + $P < .05$ vs hydroxyzine, ++ $P < .01$ vs hydroxyzine, and +++ $P < .001$ vs hydroxyzine. The doses of medications given were as follows: HYD, 25 mg; DES, 5 mg; EPI, 20 mg; and FEX, 120 mg.

Table 1. Rates of Responders to *Dermatophagoides pteronyssinus* Skin Prick Testing After Antihistamine Treatment^a

Treatment	Wheal			Erythema		
	Area by DP <7 mm ²	Diameter by PA <3 mm	Diameter by DP <3 mm	Area by PA <80 mm ²	Diameter by PA <10 mm	Diameter by DP <10 mm
Hydroxyzine, 25 mg (n=7)	5 ^b	4 ^c	4 ^c	5 ^b	4 ^c	4 ^c
Desloratadine, 5 mg (n=6)	1 ^d	0 ^c	1 ^d	1 ^d	0 ^d	1
Epinastine, 20 mg (n=6)	3	2	3	3 ^d	2	3 ^c
Fexofenadine, 120 mg (n=6)	2	2	3	2	2	3 ^c
Placebo (n=6)	0 ^e	0 ^d	0 ^d	0 ^e	0 ^d	0 ^d

Abbreviations: DP, digital photography; PA, planimetric analysis.

^a Data are given as number of responders treated with each drug. Data are given for only subjects sensitized to *D pteronyssinus* (n=31).

^b $P < .01$ vs placebo.

^c $P < .05$ vs placebo.

^d $P < .05$ vs hydroxyzine.

^e $P < .01$ vs hydroxyzine.

compares the efficacy of fgAHs with that of nsAHs by histamine or allergen skin prick testing.

The extent of histamine-induced wheal suppression by hydroxyzine and the nsAHs tested was similar to that reported in the literature. Placebo treatment resulted in no or minimal suppression of responses,^{15–21} whereas hydroxyzine was an effective suppressor.²² Desloratadine,¹⁶ fexofenadine, and epinastine¹⁷ exhibited intermediate potencies in suppressing histamine wheal responses.

Interestingly, to our knowledge, none of the AHs used in our study has been tested previously for suppressive effects on allergen prick test–induced wheal responses. However, hydroxyzine and fexofenadine have been evaluated for suppression of wheal responses induced by intradermal injection. Interestingly, these studies reported suppressive effects that were similar to those observed for hydroxyzine and fexofenadine in our study. For example, hydroxyzine, 25 mg, treatment resulted in 57% suppression of allergen-induced wheals in our study (prick testing) compared with 63% suppression reported by Cook and coworkers (intradermal testing).²³ Hydroxyzine's metabolite levocetirizine (the R enantiomer of the cetirizine racemate) has been compared with loratadine and desloratadine. Levocetirizine provided significantly greater inhibition of the histamine-induced wheal at 2 hours after administration of desloratadine.²⁴ Similar results were seen in a study comparing the effects of levocetirizine and loratadine on histamine-induced skin reactions. Flare, wheal, and itch were potently inhibited by levocetirizine, with an efficacy that exceeded that of loratadine.²⁵

Digital photography has previously been used for assessing skin prick test responses.¹² The results presented herein confirm that the use of this technique yields essentially identical results as obtained by classic macroscopic planimetric analyses. Thus, digital photography is a simple and valid method for evaluating skin prick test responses, especially in clinical trial settings, where it may be helpful to minimize interobserver differences in obtaining test results.¹²

The potency of individual AHs in suppressing histamine- and allergen-induced wheal responses cannot be directly extrapolated to their specific efficacy in the treatment of all histamine-driven conditions.²⁶ However, our findings indicate that nsAHs given at recommended doses are generally less effective than the fgAH hydroxyzine in preventing skin reactions to histamine and allergen prick testing. This suggests that nsAHs may also be less effective than fgAHs when given at recommended doses for the treatment of histamine-dependent dermatoses. This hypothesis, however, awaits confirmation, because there are no head-to-head studies, as of yet, comparing nsAH with fgAHs in, for example, urticaria.

Taken together, our findings demonstrate that hydroxyzine is a more potent inhibitor of skin prick test reactions induced by histamine and *D pteronyssinus* than desloratadine, epinastine, and fexofenadine, which suggests that daily recommended doses of hydroxyzine and nsAHs are not bioequivalent in suppressing histamine-mediated cutaneous inflammation.

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