Time-dependent inhibition of histamine-induced cutaneous responses by oral and intramuscular diphenhydramine and oral fexofenadine

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Background: Diphenhydramine is often the treatment of choice for acute urticarial or allergic reactions despite its adverse effects of sedation and impairment. Second- and third-generation histamine$_1$-antihistamines are generally devoid of these adverse effects but are typically not used because of a perceived slower onset of action.

Objective: To examine the time-dependent effects of oral fexofenadine and oral and intramuscular diphenhydramine to reduce histamine-induced wheal-and-flare responses.

Methods: Eighteen healthy patients were included in a double-blind, placebo-controlled, 3-way, randomized, crossover study with oral fexofenadine (180 mg) and oral and intramuscular diphenhydramine (50 mg). Histamine-induced skin tests were performed before and more than 6 hours subsequent to dosing. The primary end point was time to induce a 50% reduction in histamine-induced flare. Secondary end points included change from baseline at each time point in wheal-and-flare responses and area under the curve at more than 6 hours for flare.

Results: No significant differences were found in the 50% inhibitory responses of histamine-induced flares among the 3 groups ($P = .09$). No significant differences were found among the 3 groups in change from baseline at each time point except for 30 minutes during which fexofenadine had no inhibitory effect. Area under the curve analyses for wheal-and-flare responses revealed no differences among treatments at more than 6 hours.

Conclusion: Diphenhydramine tended to work more rapidly than fexofenadine, but the differences were not statistically significant. Given the adverse effect profile of diphenhydramine, but only marginal onset of action advantage, the risk-to-benefit ratio may be more favorable for oral fexofenadine when treating an acute urticarial or allergic reaction.

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INTRODUCTION

Even though the executive summary from the *Annals of Allergy, Asthma and Immunology* recommends that second-generation histamine$_1$ (H_1)–antihistamines be the treatment of choice for acute urticaria, diphenhydramine, a first-generation H_1-antihistamine, is frequently the therapy given by emergency personnel.[1,2] Diphenhydramine is inexpensive, available in both oral and parenteral routes, and perceived by many to have a quicker onset of action. In addition, health care professionals and consumers generally assume that all approved H_1-antihistamines have been shown to be efficacious and safe, but many medications in this class have not been optimally studied in randomized, double-blind, placebo-controlled trials.[3] Little evidence is available to support the opinion that first-generation antihistamines work faster or more effectively than nonsedating, second- or third-generation antihistamines in treating an acute condition.

The first-generation antihistamines have a wide pharmacologic profile: they easily cross the blood-brain barrier and bind nonselectively to H_1-receptors, but they also interact with adrenergic, serotonergic, and cholinergic receptors. Hence, many adverse effects are associated with these medications.[16] Among these effects are drowsiness, performance impairment, urinary retention, tachycardia, palpitations, and hypotension. Patients who have taken diphenhydramine have been found to be at greater risk of occupational injury than patients who have taken sedative hypnotics or narcotics.[17–21] Second-generation antihistamines are composed of large, less lipophilic molecules that do not cross the blood-brain barrier as easily and act more selectively at the H_1-receptors. Consequently, they have fewer adverse effects.[16]

We hypothesized that oral fexofenadine would work as rapidly as either oral or intramuscular diphenhydramine to inhibit an acute allergic-like reaction. If correct, this would provide more data supporting the use of safer, nonsedating, nonimpairing second- or third-generation H_1-antihistamines as opposed to first-generation antihistamines such as diphenhydramine to manage acute allergic reactions or urticaria. To test this hypothesis, we conducted a double-blind, placebo-controlled, 3-way, randomized, crossover trial of oral and intramuscular diphenhydramine and oral fexofenadine. We enrolled healthy volunteers and used as a surrogate the suppression of histamine-induced wheal-and-flare responses to evaluate if there were any differences between the medications in the onset of action to suppress cutaneous responses.

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METHODS

Patients

Healthy volunteers ages 12 to 60 years were recruited. All patients completed a written informed consent. They had to display a positive skin prick test result to histamine at an initial visit (wheal at least 5 mm greater than saline) and had to avoid prohibited medications (any medication that would suppress histamine-induced skin test reactions) for the duration of the trial. Patients were excluded if they were pregnant or lactating; had a history of moderate or severe persistent asthma, excessive alcohol intake or tobacco use, severe anaphylaxis, or anaphylactoid reaction(s); had an acute illness within 1 week of the initial visit; had a known hypersensitivity to fexofenadine or diphenhydramine; or had any other significant medical condition. They were also excluded if they were taking β-adrenergic antagonists in any form, moderate to high doses of inhaled corticosteroids, tricyclic antidepressants, or immunotherapy. The study protocol was approved by the Creighton University Medical Center Institutional Review Board.

Study Design

During an initial screening visit, the patients underwent a history and physical examination and pregnancy test if applicable. Initial histamine and saline skin prick tests were performed in duplicate on the volar surface of the forearm. Patients with a positive histamine skin test result (5 mm at least greater wheal vs isotonic sodium chloride solution) returned within 1 week for their first visit if they met all other inclusion and exclusion criteria.

The study was conducted in a double-blind, placebo-controlled, 3-way, randomized, crossover fashion. Three treatment regimens were used in this study. Each patient was given all 3 regimens, one in each of 3 intervals. There were 6 possible orders in which the treatment regimen could be administered (ie, ABC, ACB, BAC, BCA, CAB, and CBA). Eighteen patients were randomized into 3 sets of the 6 regimens by computer randomization. The sample size was determined by using a power analysis for skin test response to antihistamine with a 90% power, $\alpha = .05$, and 2 tails. The blind was maintained by an unblinded pharmacist and a backup who were privy to the blind and randomization. These 2 people had no contact with the patients and performed neither clinical nor statistical evaluations. After the final patient was enrolled and all data were entered into the database, the blind was broken. Rules for breaking the blind were for emergency cases only.

On the first visit after the screening, the patients were given histamine skin prick tests in duplicate and the wheal-and-flare responses were measured and recorded as baseline values. All patients then received in a blinded, crossover fashion a pill and an injection at each of the 3 visits for which they received medication: intramuscular diphenhydramine plus oral placebo, intramuscular placebo plus oral fexofenadine, or intramuscular placebo plus oral diphenhydramine. If they did not get the intramuscular diphenhydramine at a visit, they received an injection of saline. If they did not receive 1 of the oral medications, then they received a placebo (lactose) pill. Placebo pills and active drugs were reincapsulated by Creighton University Medical Center Pharmacy Services to preserve blinding.

Figure 1 shows the schedule of histamine skin prick tests performed in duplicate on the forearm at regular intervals at each of the 3 treatment visits. There was a minimum 7-day washout period between treatment visits. Patients were given an adverse events calendar to record any such occurrences between visits.

Skin Tests

Epicutaneous skin tests were performed in duplicate with saline and 1 mg/mL of histamine phosphate by using Hollister-Stier's QUINTIP Individual Skin Test System (Spokane, Washington). 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 patient. Skin tests were placed at least 2 cm apart. The wheal-and-flare circumferences were traced with a fine-tip rolling pen at 15 minutes and transferred to source document books with transparent tape. For precise dimensions, all wheal-and-flare areas were measured from the tracings using Digimatic calipers (Mitutoyo Corporation, Elk Grove Village, Illinois).

Statistical Analysis

The primary end point was the time at which a 50% reduction in the histamine-induced flare via skin prick testing was achieved with either diphenhydramine (50 mg intramuscularly or orally) or fexofenadine (180 mg orally). The secondary end points included measuring the percent change from baseline at each time point in the wheal-and-flare response and evaluating the global response after each treatment by calculating the wheal-and-flare surface areas under the curve after more than 6 hours. A linear-linear model was used for the analysis of variance (ANOVA) model that incorporated the 3-treatment, time-dependent, crossover design to analyze the primary and secondary end points, and $P \leq .05$ was considered statistically significant. Simple means were used to determine the means for the treatment regimens, and the means were not adjusted.

RESULTS

Nineteen patients were randomized for the study and 18 completed it. One did not complete the study because on visit

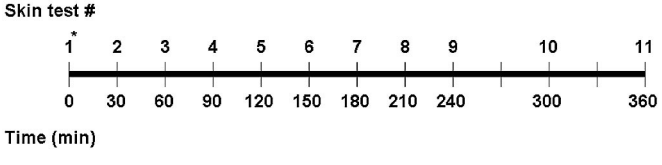

Figure 1. Skin testing was performed in duplicate at regular intervals, and the wheal-and flare responses were recorded 15 minutes after skin testing.

2 she inadvertently received 2 doses of the same medication instead of 1 being placebo. This occurrence caused no adverse event.

Figure 2 shows the time to 50% reduction in the flare induced by histamine. These mean (SEM) values were 51.7 (17.8) minutes for intramuscular diphenhydramine, 79.2 (18.4) minutes for orally diphenhydramine, and 101.2 (12.7) minutes for oral fexofenadine ($P = .09$ by repeated-measures ANOVA).

In addition, we compared the percent change from baseline at each time point by repeated ANOVA measures for wheal-and-flare responses (Figs 3 and 4). The fexofenadine group had a greater erythema response vs the other 2 treatment groups at 30 minutes ($P = .01$). No statistically significant differences were found in the flare responses at any other time point during the 6 hours among the 3 treatment groups. A statistically significant decrease was found in the wheal response in the fexofenadine group compared with both oral and intramuscular diphenhydramine at 180 ($P = .004$) and 210 minutes ($P = .0344$). Lastly, we examined the areas under the curve of histamine-induced erythema and wheal responses during the 6-hour period and found that they were not statistically significantly different ($P = .22$) for the 3 treatments (Fig 5).

DISCUSSION

This study evaluated how quickly a single dose of intramuscular or oral diphenhydramine and oral fexofenadine suppressed histamine-induced wheal-and-flare reactions. It compared parenteral and oral routes, whereas previous studies have not. It showed that there was little difference in the 3 treatment groups because they had similar histamine-induced wheal-and-flare responses overall. Intramuscular diphenhydramine tended to work more rapidly in the first hour, but thereafter fexofenadine suppressed the wheal-and-flare response more as demonstrated by comparing the percent change at each time point.

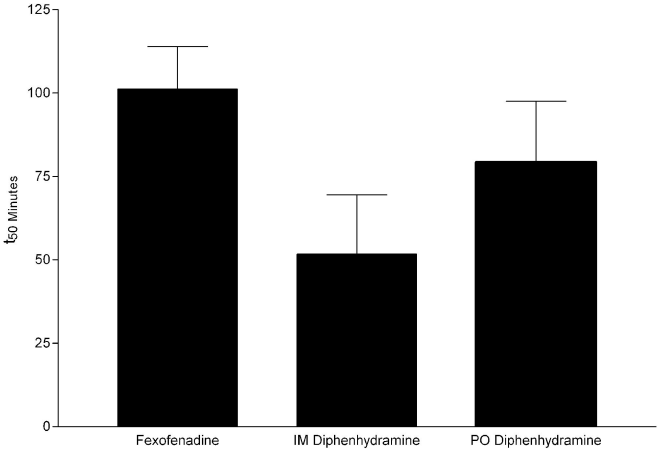

Figure 2. Time to reduce histamine-induced flare by 50% (t_{50}), the primary end point. No significant differences were found among the 3 treatments ($P = .09$). IM indicates intramuscular; PO, oral.

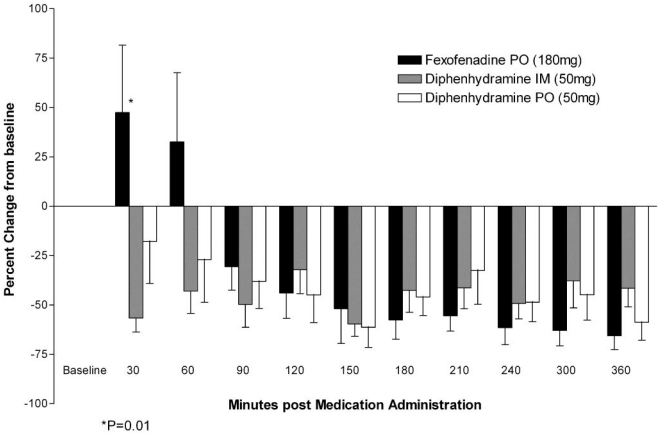

Figure 3. Percent change from baseline at each time point in the flare response. No significant differences occurred among the 3 treatments after the first 30 minutes. IM indicates intramuscular; PO, oral.

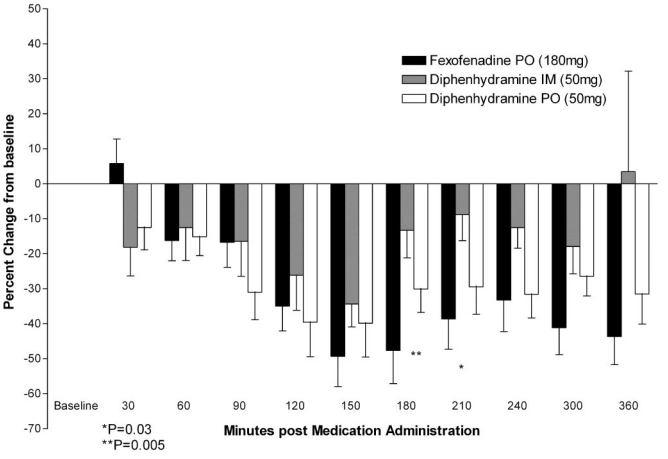

Figure 4. Percent change from baseline at each time point in the wheal response. A significant reduction was found in the size of the wheal with fexofenadine at 180 and 210 minutes compared with intramuscular (IM) and oral (PO) diphenhydramine.

The small differences in how quickly intramuscular diphenhydramine and fexofenadine work may be partially explained by the routes they were given (parenteral vs oral). Intramuscular diphenhydramine tended to work faster. The average time to peak concentration in the serum is similar for oral diphenhydramine and oral fexofenadine: 2 to 4 hours and 2.6 hours, respectively.[22] However, we were unable to find published data on this for the parenteral route of diphenhydramine. Parenteral diphenhydramine would likely have a shorter time to reach peak serum concentration.

Our data are consistent with a study that did not show significant differences in the suppression of the wheal-and-flare response at 1 hour after dosing with oral fexofenadine (120 mg) or oral diphenhydramine (50 mg).[12,13] However, we

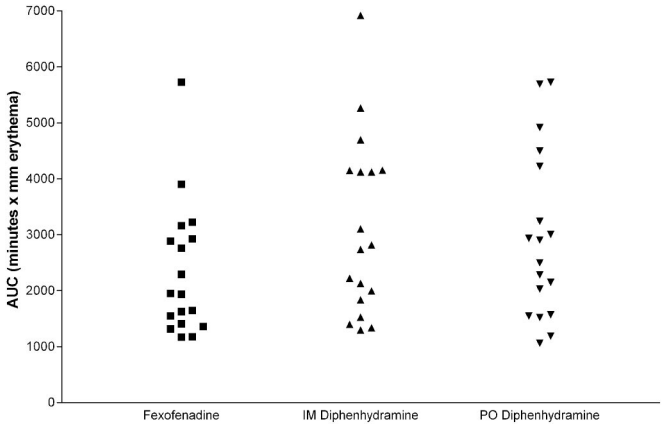

Figure 5. Area under the curve (AUC) after more than 6 hours for histamine-induced flare. No statistically significant differences were found among the 3 treatments. IM indicates intramuscular; PO, oral.

found that at 3 hours, fexofenadine significantly suppressed the wheal-and-flare response more than oral diphenhydramine. Simons et al[12,13] also showed that fexofenadine penetrated the skin to a significantly greater extent than oral diphenhydramine. Furthermore, a number of studies have compared the relative potency of many H_1-antihistamines by measuring suppression of the histamine-induced wheal-and-flare response.[7–11]

When treating someone with an acute allergic reaction or urticaria, one must not only consider which treatments are most effective but also the adverse effects of those medications. Hence, it may be prudent to consider the risks and benefits of using first-generation vs second- or third-generation antihistamines. In addition to sedation and anticholinergic adverse effects, evidence shows that first-generation antihistamines such as diphenhydramine impair psychomotor performance or measures of driving performance under experimental conditions more than alcohol.[14–16] They may also lead to an increased risk of serious injury.[17] According to one study, the greatest increase in work-related injury occurred among users of sedating antihistamines, with a 1.5-times increased risk of occupational injury. Furthermore, the risk of injury after first-generation antihistamine use was greater than that after the use of sedative hypnotics or narcotics.[18–21]

Patients can readily detect drowsiness but not so much impairment. Studies of a variety of central nervous system (CNS) depressants have consistently shown that patients treated with these drugs cannot reliably or accurately determine how well they are driving or performing other complex tasks.[20] Indeed, there are data implicating these medications as a cause of fatal traffic accidents.[18] The CNS effects can linger longer than 8 hours, and even with evening dosing, subjective drowsiness still occurs the morning after use. Tolerance does not necessarily develop, and impairment of CNS function occurs in the absence of obvious symptoms. Given the adverse effect profile and the risk of injury with first-generation antihistamines such as diphenhydramine, but only marginal onset of action advantage, the risk-to-benefit ratio may be more favorable for oral second- or third-generation antihistamines such as fexofenadine.

Patients with a history of severe anaphylaxis or anaphylactoid reactions were excluded from this study. If a patient presents to the emergency department with symptoms consistent with this type of serious life-threatening reaction, the treatment of choice is still epinephrine and parenteral first-generation antihistamines. Oral second- or third-generation antihistamines should not be used in this situation until confirmatory data are available as to equivalence in onset of action and efficacy.

A limitation that might be considered in this study was that impairment was not evaluated at the same time the skin tests were performed. This was not done because we believed that the adverse effects of diphenhydramine, and lack thereof for fexofenadine, have been well documented. In addition, for unknown reasons, the flare response significantly increased at 30 minutes after drug administration in the fexofenadine group. One possible explanation for this is that 7 different nurses documented the size of the wheal-and-flare responses. This may have increased the chance of inconsistencies by which they were recorded. There may have been more consistency had 1 person been able to perform all the recordings. Furthermore, we may have been able to achieve more consistent results if we had a larger sample size.

In conclusion, intramuscular and, to a lesser extent, oral diphenhydramine tended to work more rapidly than fexofenadine, but overall the differences were not statistically significant. Given the adverse effect profile with diphenhydramine, but only marginal onset of action advantage, the risk-to-benefit ratio may be more favorable for oral fexofenadine when treating an acute urticarial or allergic reaction. Future studies comparing the effects of different first- and second- or third-generation antihistamines to concomitantly evaluate impairment and the antipruritic effects with the ability to suppress an acute allergic reaction might be in order. For example, comparing cetirizine to the agents used in this study would be interesting to examine since its effective suppression of histamine-induced wheal-and-flare reactions is well documented. In addition, consideration may be given to examining how antihistamines available in rapid orally disintegrating tablets, such as loratadine or desloratadine, compare with intramuscular diphenhydramine.

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