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Intravenous Cetirizine Versus Intravenous Diphenhydramine for the Treatment of Acute Urticaria: A Phase III Randomized Controlled Noninferiority Trial

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Study objective: Acute urticaria is a frequent presentation in emergency departments (EDs), urgent care centers, and other clinical arenas. Treatment options are limited if diphenhydramine is the only intravenous antihistamine offered because of its short duration of action and well-known adverse effects. We evaluate cetirizine injection, the first second-generation injectable antihistamine, for acute urticaria in this multicenter, randomized, noninferiority, phase 3 clinical trial.

Methods: Adult patients presenting to EDs and urgent care centers with acute urticaria requiring an intravenous antihistamine were randomized to either intravenous cetirizine 10 mg or intravenous diphenhydramine 50 mg. The primary endpoint was the 2-hour pruritus score change from baseline, with time spent in treatment center and rate of return to treatment centers as key secondary endpoints. Frequency of sedation and anticholinergic adverse effects were also recorded.

Results: Among 262 enrolled patients, the 2-hour pruritus score change from baseline for intravenous cetirizine was statistically noninferior to that for intravenous diphenhydramine (−1.6 versus −1.5; 95% confidence interval −0.1 to 0.3), and in favor of cetirizine. Treatment differences also favored cetirizine for mean time spent in treatment center (1.7 versus 2.1 hours; P=.005), return to treatment center (5.5% versus 14.1%; P=.02), lower change from baseline sedation score at 2 hours (0.1 versus 0.5; P=.03), and adverse event rate (3.9% versus 13.3%).

Conclusion: Intravenous cetirizine is an effective alternative to intravenous diphenhydramine for treating acute urticaria, with benefits of less sedation, fewer adverse events, shorter time spent in treatment center, and lower rates of revisit to treatment center. [Ann Emerg Med. 2020;■:1-12.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Acute urticaria is frequently observed in emergency departments (EDs), urgent care centers, inpatient hospital units, and other clinical arenas throughout the health care system (oncology, dermatology, rheumatology, radiation, and general medicine clinics). Acute urticaria is a vascular skin reaction marked by transient, erythematous, intensely pruritic raised wheals or similar rash with or without angioedema.[1] It characteristically appears quickly, resolves during hours, and may repeatedly recur for up to 6 weeks.[2] Nearly 450,000 visits are made annually to EDs for urticaria, according to the 2016 US National Hospital Ambulatory Medical Care Survey.[3] Acute urticaria typically responds to pharmacotherapy, with antihistamines being the first-line treatment.[4] The parenteral route of administration is often preferred to provide rapid onset of action.[1]

Importance

Until recently, the first-generation short-acting antihistamine diphenhydramine was the only antihistamine available for intravenous administration. Its adverse event profile includes sedation and other anticholinergic adverse effects (eg, urinary retention, constipation, dry mouth, other central nervous system impairment)[5] that may

Editor's Capsule Summary

What is already known on this topic

Parenteral diphenhydramine is a long-standing but sedating option for treating acute urticaria.

What question this study addressed

How does intravenous cetirizine 10 mg, a newer antihistamine, compare with intravenous diphenhydramine 50 mg in acute treatment of acute urticaria?

What this study adds to our knowledge

In a 262-subject, randomized, blinded trial in either an emergency department or urgent care setting, cetirizine was noninferior to diphenhydramine in relieving itch at 2 hours, with shorter care intervals, decreased sedation, and lower adverse events rates.

How this is relevant to clinical practice

This agent is an option in the narrow group of urticaria patients needing parenteral therapy.

complicate clinical management and delay ED or urgent care discharge.[1,4,6-9]

Hydroxyzine, another first-generation antihistamine, is contraindicated for intravenous use. It can be used only as an intramuscular injection; additionally, hydroxyzine injection is not approved by the Food and Drug Administration for the treatment of allergic reaction or acute urticaria.[10] It has an adverse effect profile similar to that of diphenhydramine, including sedation and cognitive impairment.

First-generation antihistamines are known to cause significant driving impairment comparable to or greater than that of alcohol intoxication (blood alcohol level of 0.1%), leading to recommendations that patients not drive after treatment.[11-13] The second-generation antihistamines (including cetirizine, loratadine, and fexofenadine) are associated with a decreased rate of sedation, a 24-hour duration of action, minimal anticholinergic effects, as well as lower rates of other adverse effects associated with first-generation antihistamines.[1,6,9,14] Because it is not feasible to conduct a placebo-controlled clinical trial with patients with an acute condition, regulatory agencies and investigator review boards suggest conducting a noninferiority clinical trial. In a phase 2 clinical study (Efficacy Trials for the Treatment of Acute Urticaria 2), intravenous cetirizine achieved acute urticaria symptom score reductions similar to those of intravenous diphenhydramine while allowing less time spent in treatment centers because of decreased sedation levels. Intravenous cetirizine also resulted in lower symptom recurrence rates.

Goals of This Investigation

Whereas oral cetirizine is indicated for chronic urticaria, intravenous cetirizine is indicated for the treatment of acute urticaria associated with acute allergic reactions. These are different indications for different conditions, although with similarities involving histamine release. This phase 3 multicenter randomized trial (ETTAU-03) evaluated the efficacy and other treatment outcomes of intravenous cetirizine versus intravenous diphenhydramine in patients with acute urticaria. The primary objective was to establish the noninferiority of intravenous cetirizine relative to intravenous diphenhydramine in reducing the patient-reported pruritus severity score at 2 hours after treatment of acute urticaria. The key secondary efficacy and clinical measures of this study were the time spent at the treating facility and need to return to a treatment center, with a number of other assessed outcomes that included physician-rated extent of urticaria and erythema scores, pruritus treatment success rates, effective treatment rates, rescue medication use, sedation, and adverse events.

MATERIALS AND METHODS

Study Design and Setting

This was a multicenter, double-blind, randomized, phase 3 clinical trial with a parallel-group, active-controlled, noninferiority design. The study was conducted at 19 sites in the United States and Canada. Patients were considered for enrollment if they presented with acute urticaria to EDs or urgent care centers. Relevant institutional review boards at each participating site granted approval for the conduct of this trial. Written informed consent was obtained from each patient through an approved standard process.

Selection of Participants

Inclusion criteria for the trial were patients aged 18 years or older who required an antihistamine to relieve symptoms of acute urticaria (based on the clinical judgment of the investigator), with a patient-rated pruritus severity score greater than or equal to 1, and willing and able to give informed consent. Patients who, according to investigator assessment, had acute urticaria caused by a reaction to a current medication (eg, antibiotics, nonsteroidal anti-inflammatory drugs) but who could stop the medication after presenting to the site were eligible. Patients who presented with acute urticaria together with angioedema or

anaphylaxis, provided that urticaria was still present after initial treatment and alleviation of anaphylaxis symptoms, were qualified to be enrolled.

Patients were excluded if they had anaphylaxis before the acute anaphylactic symptoms were treated. Other key exclusion criteria were contraindication, known allergy, or suspected intolerability to study medication, receipt of an H_1 or H_2 antagonist or doxepin in the previous 2 hours, corticosteroids (any route) in the previous 4 hours, epinephrine in the previous 20 minutes, and concomitant use of *p*-glycoprotein inhibitors (including amiodarone, clarithromycin, erythromycin, ketoconazole, quinidine, and saquinavir).

Interventions

Eligible patients were randomized in a 1:1 ratio to receive a single dose of cetirizine 10 mg or diphenhydramine 50 mg, each administered as a single 1.0-mL injection by an approximately 2-minute intravenous push.

Additional medications (epinephrine, corticosteroids, etc) were allowed as rescue drugs if deemed necessary by the investigator or designee. However, if the patient was without medical complication, all efforts were made to have him or her complete at least the 1-hour assessment before administration of any rescue medication. If patients required rescue medication shortly after study drug administration (eg, within approximately 10 to 15 minutes), this indicated that they may have had anaphylaxis, and they were therefore immediately withdrawn from the study.

Treatment drugs intravenous cetirizine and intravenous diphenhydramine were visually identical clear aqueous solutions in 2-mL amber vials containing 1 mL of medication. Treatment drugs were prerandomized and preblinded by the sponsor's contract research organization, according to a centralized randomization schedule (generating a randomization list in blocks of 4), before being delivered to each investigational site. A treatment vial, consisting of one vial of either intravenous cetirizine or intravenous diphenhydramine, was packaged and labeled by the randomization number, with a blinded label to conceal the product name. To further maintain blinding, a staff member who was not involved in patient management or outcome assessment was responsible for drawing up the randomized medication into a syringe for administration. The health care professional involved in patient management and outcome assessment was completely blinded.

Treatment group assignment was denoted by sequential numbers within a site randomization list, which was kept secured by the contract research organization until the study blind was broken. To preserve the blinding of the study at the investigational site, site personnel did not have access to the randomization code and treatment assignments before database lock. Study blinding was to be broken only if the identity of the study drug was considered vital for the clinical management of the patient.

Methods of Measurement

Clinical efficacy measures included the patient-rated pruritus severity score (primary outcome measure; see later text) and sedation score; the physician-rated extent of urticaria/erythema score, assessed at baseline and 1 and 2 hours posttreatment; and time to discharge. The patient-rated pruritus score was adapted from a previously validated scoring scale for chronic urticaria (to our knowledge, acute urticaria had never been studied in a pivotal clinical trial before the study of cetirizine reported here), with a severity score of 0 to 3 (0=none, 1=mild, 2=moderate, and 3=severe) in response to the question, How severely are your hives itching at the moment?[15] The investigators also provided extent of urticaria/erythema scores (percentage of body area affected and the intensity of redness, using a burn wound assessment chart) on a 0-to-3 scale, and an assessment of whether a patient was "effectively treated." Use of rescue medications (epinephrine, bronchodilators, corticosteroids, etc) and additional pharmacologic agents (including the reason for use, symptom recurrence or additional symptom occurrence, and the ability to return to normal activity) was assessed with a questionnaire given at follow-up telephone calls 24 hours after discharge, 48 hours after discharge, or both. The patient-rated sedation score was recorded by research staff according to a severity score of 0 to 3 (0=none [not drowsy at all], 1=mild [slightly drowsy], 2=moderate [quite drowsy], and 3=severe [extremely drowsy]) in response to the question, How drowsy do you feel at the moment? The time spent at the treatment center (time from treatment administration to readiness for discharge) and the need to return to the treatment center after study discharge (ie, a second visit after discharge) were also assessed, with the latter determined by patient follow-up telephone calls. Safety was evaluated by monitoring vital signs and adverse events (at site arrival, baseline, 1 and 2 hours postadministration, and discharge), with adverse events subsequently recorded 24 hours and 48 hours after discharge, and for up to 28 days after treatment through patient self-reporting.

Outcome Measures

The primary efficacy endpoint was the change in patient-rated pruritus score from baseline to 2 hours after

treatment administration. Two key secondary efficacy outcomes were percentage of patients who returned to any ED or clinic, and the time spent at the treatment center (time from treatment administration to discharge readiness). Additional secondary outcomes reported included change from baseline to 2 hours in physician-rated extent of urticaria/erythema scores; percentage of patients needing rescue medication, pruritus treatment success, effectively treated, returning to normal activity, and symptom recurrence after discharge; patient-reported sedation scores; and adverse event rates. Pruritus treatment success was a patient-reported outcome defined as a reduction in pruritus severity score at 2 hours of at least 1 unit compared with baseline. This contrasted with the measure of effectively treated patients, a physician-reported outcome based on the investigator's opinion of yes or no.

Primary Data Analysis

A sample size of 127 patients per arm (total N=254) was needed to provide 90% statistical power to determine whether intravenous cetirizine would be noninferior to intravenous diphenhydramine, as calculated from the previous ETTAU-02 study. The sample size was established according to the assumption of –0.5 as the noninferiority margin for the primary outcome measure of pruritis score. Agreement with the regulatory agency on –0.5 as the noninferiority margin was based on sponsor's phase 2 clinical results from the intravenous cetirizine versus intravenous diphenhydramine study, which showed that the 95% confidence interval (CI) around the change from baseline after 2 hours of treatment with diphenhydramine spanned the width of ±0.5 units. The null hypothesis was that intravenous cetirizine was inferior to intravenous diphenhydramine if the treatment difference in the change from baseline in patient-rated pruritus score at 2 hours had a 95% CI that included –0.5.

The primary analysis was performed for the intention-to-treat population (all randomized patients who were given a subject identification number with intention to treat with blinded study drug) with the last observation carried forward imputation method used to impute 2-hour scores if patients were discharged before this assessment. The point estimate of treatment differences of the change from baseline of 2-hour patient-rated pruritus severity score and the 95% CIs were to be calculated with a 2-sided *t* test from a generalized linear mixed-effects model to adjust for any heterogeneity of treatment variance, to adjust for imbalance in numbers of patients in each treatment, and to adequately model the resulting interval outcome. The model initially consisted of the change from baseline at 2 hours as the dependent variable and site, treatment, and site×treatment as fixed effects. It was observed in this a priori analysis that site effects contributed greatly to the variability of the outcome; however, there were no site×treatment interactions. In addition, baseline pruritus scores were found to be a significant covariate. Because the number of sites was relatively large for a fixed-effect model with site and because site×treatment interactions were not significant, an additional analysis was performed on the primary analysis intention-to-treat population, using a model that allowed site to be a random factor and included baseline pruritus as a covariate. Results of the model, considered to be a better fit than the a priori model according to goodness-of-fit statistics, are reported here. The 2 key secondary efficacy outcomes were adjusted for multiplicity to minimize type I error; no adjustments for multiplicity were made for the other secondary endpoints. Safety analyses included patients who received blinded study drug, regardless of whether they completed all assessments, withdrew, or were discontinued by the investigator. Evaluation of the primary endpoint based on age was performed as a post hoc analysis. All statistical analyses and summaries were performed with SAS (version 9.4; SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Subjects

Of 268 screened patients, a total of 262 eligible ones were randomized to intravenous diphenhydramine (n=135) or intravenous cetirizine (n=127) at 19 study centers in North America (Figure 1) between March 2, 2017, and April 14, 2018, for whom baseline demographic and disease characteristics are summarized in Table 1. The baseline characteristics between groups were comparable. Of the 19 sites, 17 were EDs and 2 were urgent care centers. Of the 262 patients enrolled, 222 (84.7%) presented to hospital EDs and 40 (15.3%) presented to urgent care centers. No patients presenting with anaphylaxis participated in the trial.

All randomized patients were included in both the intention-to-treat efficacy and safety populations (Figure 1).

The primary efficacy data are presented in Table 2 and Figure 2. With a mean change from baseline in patient-rated pruritus severity score of –1.6 (SD 0.9) for intravenous-cetirizine-treated patients and –1.5 (SD 1.0) for intravenous-diphenhydramine-treated patients, the least squares estimated treatment difference was 0.1 (95% CI –0.1 to 0.3; *P*=.35). Because the lower bound of the 95% CI for the treatment difference did not include –0.5,

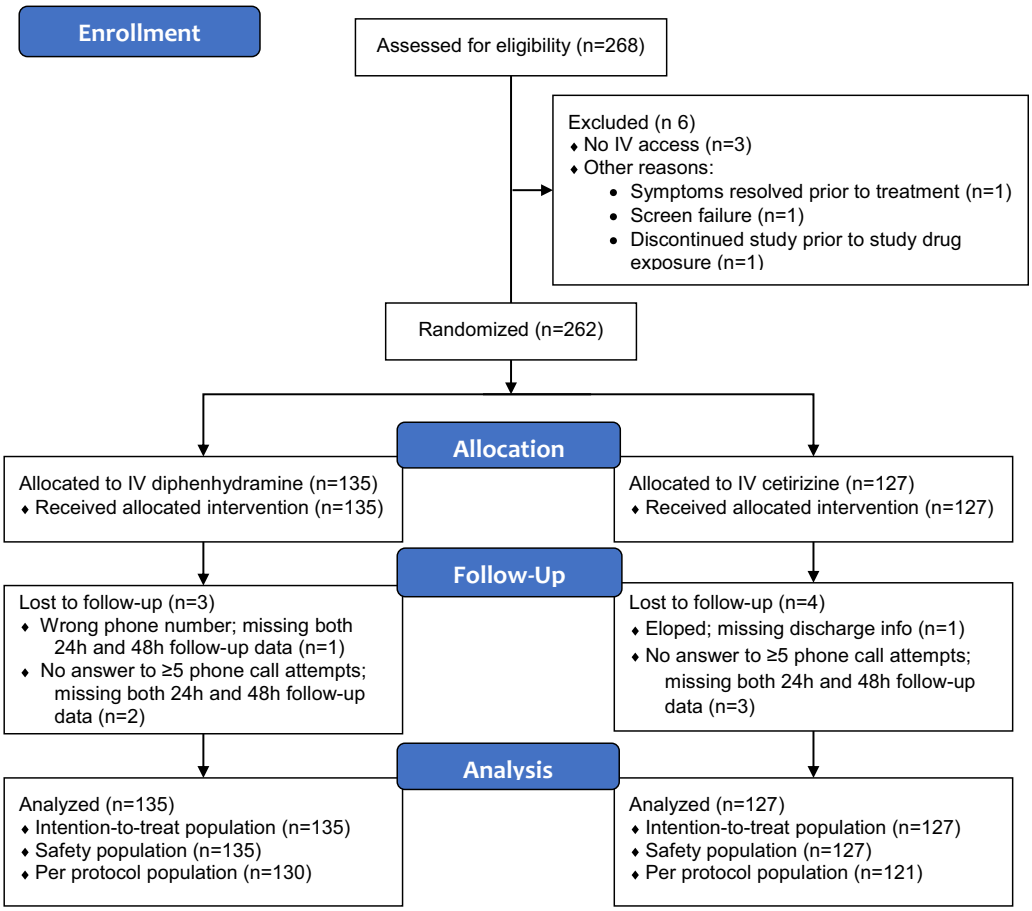

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of study enrollment. The intention-to-treat (ITT) population included any patient who was randomized and given a subject identification number with intention to treat with one of the blinded study drugs. The safety population included any patients in the intention-to-treat population who actually received a blinded study drug, regardless of whether they completed all assessments, withdrew, or were discontinued by the investigator. The per-protocol population included patients in the safety population who completed all necessary assessments without any incidence that would potentially affect the ability to objectively assess treatment response (discontinuation, protocol deviation, etc).

effectiveness of intravenous cetirizine was determined to be statistically noninferior to that of intravenous diphenhydramine. There were also no treatment differences for the primary efficacy outcome based on patients' age (<65 and ≥65 years) (Table 3).

Statistically significant differences favoring intravenous cetirizine over intravenous diphenhydramine were observed with respect to the key secondary outcomes as shown in Table 4: both the time spent in the treating facility and the proportion of patients needing to return to a treatment center within 24 hours and 48 hours of patient discharge, captured by postdischarge patient follow-up.

Other secondary efficacy measures are also shown in Table 4. Mean changes from baseline to 2-hour physician-rated urticaria/erythema scores were similar between intravenous cetirizine and intravenous diphenhydramine (–0.6 [SD 0.6] versus -0.5 [SD 0.6]).

The number of patients whose pruritus was successfully treated was similar for both treatment groups. However, the number of "effectively treated" patients according to physician assessment was higher in the intravenous cetirizine treatment group (P=.02). There were fewer patients in the intravenous cetirizine group who required rescue drug usage compared with the intravenous diphenhydramine group (P=.016). The most common rescue medication was corticosteroids in both groups (intravenous cetirizine, n=15 [12%], versus intravenous diphenhydramine, n=31 [23%]), with infrequent epinephrine administration (intravenous cetirizine, n=1 [1%], versus intravenous diphenhydramine, n=3 [2%]).

After treatment, patient-rated sedation scores increased in both treatment groups during the first hour (Figure 3). Mean sedation score increases from baseline in the intravenous cetirizine group were significantly smaller than

Table 1. Characteristics of patients receiving intravenous diphenhydramine or intravenous cetirizine for treatment of acute urticaria.

Characteristic	IV Diphenhydramine 50 mg (n=135)	IV Cetirizine 10 mg (n=127)
Age, y		
Mean (SD)	39.2 (16.0)	39.0 (16.3)
Median	37.0	36.0
Range	18–87	18–92
Sex, No. (%)		
Women	88 (65)	77 (61)
Men	47 (35)	50 (39)
Race, No. (%)		
White	62 (46)	64 (50)
Black	44 (33)	41 (32)
Asian	5 (4)	4 (3)
Other	3 (2)	2 (2)
Native Hawaiian or other Pacific Islander	0	1 (1)
Ethnicity, No (%)		
white, Hispanic or Latino	0	1 (1)
Nonwhite, Hispanic or Latino	21 (16)	14 (11)
Presenting complaint(s), No. (%)		
Urticaria only	118 (87)	110 (87)
Urticaria+angioedema	16 (12)	16 (12)
Angioedema only	1 (1)	1 (1)
Known allergies, No. (%)		
None	102 (76)	100 (79)
Antibiotic drugs*	13 (10)	10 (8)
Other medications†	9 (7)	5 (4)
Food‡	4 (3)	9 (7)
Other§	9 (7)	3 (2)

IV, Intravenous.
Intention-to-treat population. Percentages may add up to more than 100% because of rounding or multiple known allergies in a single patient.
*IV diphenhydramine arm: amoxicillin (3), sulfa (2), vancomycin (2), sulfa (1), cefprozil (1), nitrofurantoin (1), levofloxacin (1), neomycin/polymyxin/hydrocortisone otic solution (1), and unspecified antibiotic for tooth infection (1). IV cetirizine arm: sulfa (4), amoxicillin (2), sulfa/penicillin (1), fluconazole (1), vancomycin (1), and daptomycin (1).
†IV diphenhydramine arm: naproxen (1), aspirin (1), liraglutide (1), Tylenol Cold and Flu (1), fentanyl (1), cocaine/crack (1), escitalopram (1), amitriptyline (1), iron sucrose supplement (1). IV cetirizine arm: lamotrigine (1), prednisone (1), meloxicam (1), naproxen (1), and loperamide (1).
‡IV diphenhydramine arm: dairy/eggs/peanuts (1), nuts/seafood (1), shrimp (1), and blueberry pancakes (1). IV cetirizine arm: peanuts (2), shellfish (2), shrimp (1), fish/seafood (1), milk/inflammatory food (1), kiwi (1), and white bread (1).
§IV diphenhydramine arm: IV contrast (3), hair dye (1), lotion (1), perfume (1), new razor product (1), unspecified plant at home (1), and poison ivy (1). IV cetirizine arm: IV contrast (1), bee stings (1), and hair dye (1).

those observed in the intravenous diphenhydramine group at 1-hour assessment (0.2 [SD 0.8] versus 0.7 [SD 0.9]; *P*=.003), 2-hour assessment (0.1 [SD 0.8] versus 0.5 [SD 0.9]; *P*=.03), and discharge (0.1 [SD 0.8] versus 0.5 [SD 0.9]; *P*=.04). The mean sedation score increases were also smaller in the intravenous cetirizine group versus the intravenous diphenhydramine group in patients aged 65 years or older at 1-hour assessment (0.0 [SD 0.5] versus 0.7 [SD 0.9]), 2-hour assessment (0.0 [SD 0.7] versus 0.3 [SD 0.9]), and discharge (0.0 [SD 0.7] versus 0.4 [SD 0.7]).

Overall, 31 adverse events were reported, 24 in the intravenous diphenhydramine group and 7 in the intravenous cetirizine group. Twenty-three patients (8.8%) experienced at least 1 adverse event, including 18 (13.3%) intravenous-diphenhydramine-treated patients and 5 (3.9%) intravenous-cetirizine-treated patients. Dizziness and nausea were the most common adverse events, all occurring in the intravenous diphenhydramine group (dizziness: n=6 [4.4%]; nausea: n=4 [3.0%]) (Table 5). None of the adverse

Table 2. Primary efficacy endpoints among patients receiving intravenous diphenhydramine or intravenous cetirizine for treatment of acute urticaria.

Primary Efficacy Endpoint (Tested for Noninferiority)	IV Diphenhydramine 50 mg (n=135)	IV Cetirizine 10 mg (n=127)	Difference (95% CI)
Patient-rated pruritus score at baseline			
Mean (SD)	2.2 (0.7)	2.2 (0.7)	
Patient-rated pruritis score at 2 h			
Effect size	0.7	0.7	
Mean (SD)	0.7 (0.9)	0.6 (0.9)	
No. (%) of patients with 2-h LOCF*	78 (57.7)	78 (61.4)	
Patient-rated pruritus score change from baseline at 2 h			
Effect size	−1.5	−1.7	
Mean (SD)	−1.5 (1.0)	−1.6 (0.9)	0.1 (−0.1 to 0.3)†

LOCF, Last observation carried forward.
Intention-to-treat population, last observation carried forward.
*Last observation carried forward was used when a patient was discharged before the 2-hour assessment.
†Because the lower bound of the 95% CI for the treatment difference was greater than −0.5, effectiveness of intravenous cetirizine was demonstrated to be noninferior to that of intravenous diphenhydramine.

events in the intravenous cetirizine group occurred in greater than one patient.

There were 10 patients who developed adverse events related to study treatment. Nine patients were receiving intravenous diphenhydramine and one was receiving intravenous cetirizine. Patients reported dizziness (n=5) and nausea (n=3) as the most common intravenous-diphenhydramine-related adverse events. Regarding intravenous-cetirizine-related adverse events, one patient developed a combination of dysgeusia, paresthesia, and sensation of warmth. No overall differences in safety were observed in patients aged 65 years or older versus younger patients.

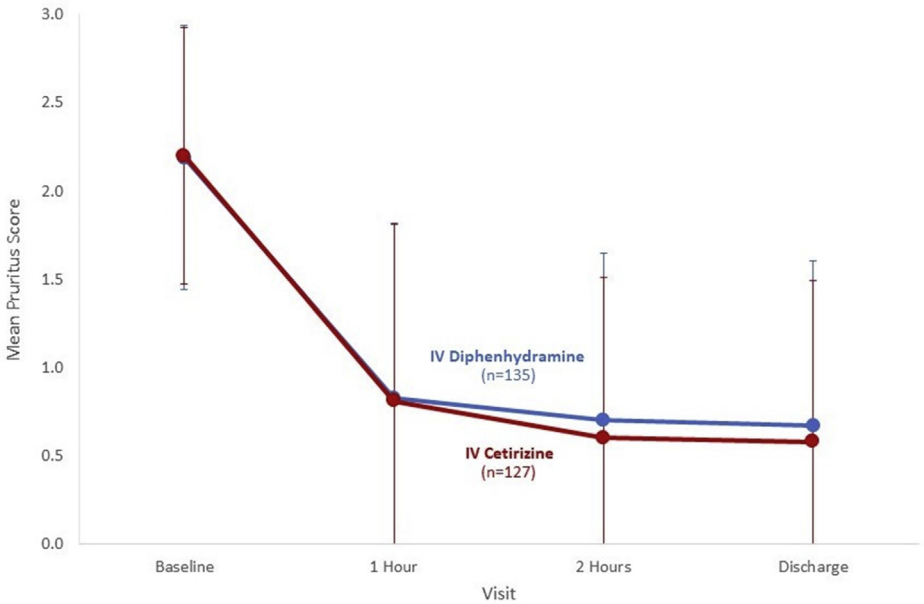

Figure 2. Patient-rated pruritus score and change by visit. Intention-to-treat population. The adjusted treatment difference between intravenous diphenhydramine versus intravenous cetirizine was 0.1 (*P*=.65) at baseline, −0.1 (*P*=.76) at 1 hour, 0.1 (*P*=.47) at 2 hours, and 0.1 (*P*=.50) at discharge.

Table 3. Post hoc analysis of primary efficacy endpoints among elderly patients receiving intravenous diphenhydramine or intravenous cetirizine for treatment of acute urticaria.

Primary Efficacy Endpoint	IV Diphenhydramine 50 mg	IV Cetirizine 10 mg	Difference (95% CI); *P* Value
Patient-rated pruritus score change from baseline at 2 h			
<65 y			
No.	126	118	
Effect size	−1.6	−1.7	0.1(−0.1 to 0.3);
Mean (SD)	−1.5 (1.0)	−1.6 (0.9)	.55*
≥65 y			
No.	9	9	
Effect size	−1.1	−2.0	0.9 (−0.2 to 2.0);
Mean (SD)	−1.1 (1.1)	−2.0 (1.0)	.099*

Intention-to-treat population, last observation carried forward.
*Based on a generalized linear mixed-effects model 2-sided *t* test. The model consisted of the change from baseline at 2 hours as the dependent variable and treatment as the fixed effect, baseline pruritus score as a covariate, and site as a random effect.

One serious adverse event of anaphylactic reaction in the intravenous diphenhydramine group was reported in the study. This event was moderate in severity and assessed by the investigator as not related to study treatment. No adverse events leading to study withdrawal and no deaths occurred during the study.

LIMITATIONS

We acknowledge several limitations, including the nature of the acute disease, which made a placebo-controlled trial unfeasible. To our knowledge, there is no history of a registration pivotal clinical trial for the indication of acute urticaria. Therefore, the clinical

Table 4. Secondary efficacy endpoints among patients receiving intravenous diphenhydramine or intravenous cetirizine for treatment of acute urticaria.

Endpoint	IV Diphenhydramine 50 mg (n=135)	IV Cetirizine 10 mg (n=127)	*P* Value
Key secondary efficacy endpoints (tested for superiority)			
Patients returning to any ED or clinic within 24 h of patient discharge, No. (%)	15 (11.1)	5 (3.9)	.04*
Patients returning to any ED or clinic within 48 h of patient discharge, No. (%)	19 (14.1)	7 (5.5)	.02*
Time spent at treatment center, h†			
Effect size	1.9	2.0	
Mean (SD)	2.1 (1.1)	1.7 (0.9)	.005‡
Other secondary efficacy endpoints (tested for superiority)			
Physician-rated extent of urticaria/erythema score reduction from baseline at 2 h			
Effect size	−0.8	−1.0	
Mean (SD)	−0.5 (0.6)	−0.6 (0.6)	.36§
Patients with pruritus treatment success, No. (%)	111 (82.2)	110 (86.6)	.40*
Effectively treated patients,‖ No. (%)	93 (68.9)	103 (81.1)	.02*
Patients needing rescue medication, No. (%)	37 (27.4)	19 (15.0)	.02*

Intention-to-treat population, last observation carried forward.
*Based on Fisher's exact 2-sided test.
†Median was 2.0 h for intravenous diphenhydramine (n=133) versus 1.4 h for intravenous cetirizine (n=120).
‡Based on a generalized linear mixed-effects model 2-sided *t* test. The model consisted of time as the dependent variable and treatment as the fixed effect, baseline pruritus score as a covariate, and site as a random effect.
§Based on a generalized linear mixed-effects model 2-sided *t* test. The model consisted of time as the dependent variable and site, treatment, and site×treatment as fixed effects.
‖Based on physician's assessment at readiness for discharge.

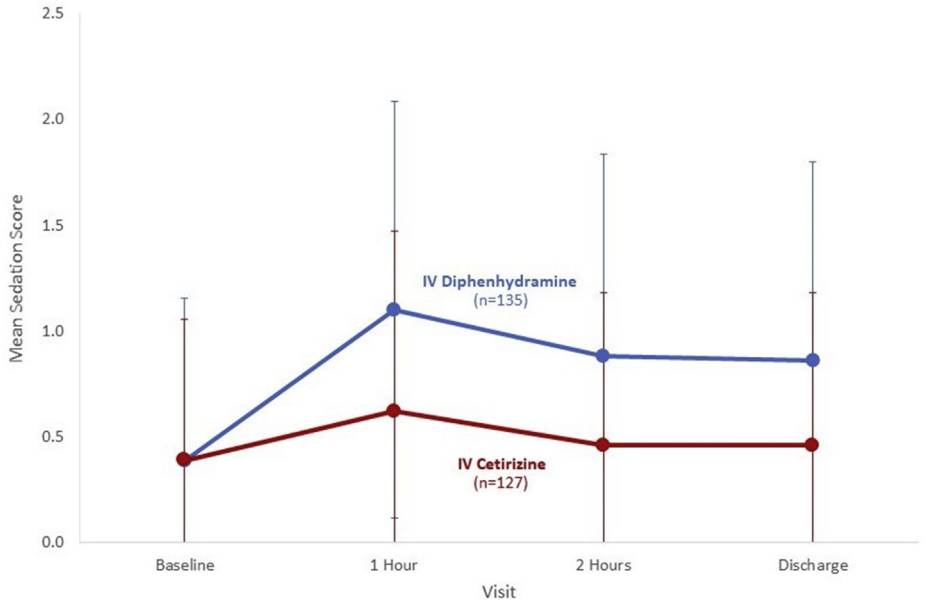

Figure 3. Patient-rated sedation score and change by visit. Intention-to-treat population. At 1 hour, the change in mean sedation score was 0.7 (SD 0.9) for intravenous diphenhydramine versus 0.2 (SD 0.8) for intravenous cetirizine (P=.003). At 2 hours, the change in mean sedation score was 0.5 (SD 0.9) for intravenous diphenhydramine versus 0.1 (SD 0.8) for intravenous cetirizine (P=.03). At discharge, the change in mean sedation score was 0.5 (SD 0.9) for intravenous diphenhydramine versus 0.1 (SD 0.8) for intravenous cetirizine (P=.04).

measurements and rating scales used in this study were a result of discussion with the Food and Drug Administration. These may have some subjectivity; however, the results from a pilot study[16] using these measurements and rating scales were similar. Anaphylactic patients were excluded from the study when the anaphylactic symptoms were still present; however, when anaphylactic symptoms had been controlled, enrollment in the study was allowed. In actual medical practice in EDs, intravenous diphenhydramine (among other drugs) is commonly used together with epinephrine, the first-line therapy for anaphylaxis. The formulation of cetirizine evaluated in this trial is currently for intravenous use only; therefore, another limitation is that our results are not applicable to clinical situations in which intramuscular administration of antihistamines is preferred, either institutionally or by individual practitioners. Finally, although assessment of treatment effects based on specific underlying cause(s) of urticaria was not a goal of this study, it is possible that response to therapy depends on underlying pathophysiology.

DISCUSSION

Early clinical development of intravenous cetirizine revealed a pharmacokinetic profile that would be favorable for an acute condition (ie, acute urticaria commonly observed in EDs,[14] urgent care centers, inpatient hospital units, and oncology or other specialty or general medicine clinics) requiring an immediate onset of action.[17] Our phase 3 results showed that although the effectiveness (score reductions on pruritus and extent of urticaria/erythema) of the treatments was comparable, intravenous cetirizine was associated with fewer adverse events, less sedation, shorter time in the treatment center, lower revisit rate to the treatment center, and less rescue drug usage, symptom recurrence, and additional medication usage.The safety and tolerability of cetirizine have been well established during the past 30 years,[18] and clinical data from this phase 3 study of intravenous cetirizine support a safety profile similar to that of oral cetirizine. In the current study, there were significantly fewer overall adverse events reported in patients treated with intravenous cetirizine compared with intravenous diphenhydramine. Dizziness and nausea were the most common adverse events in the study. Dizziness is a known adverse effect of diphenhydramine,[5] and all events of this type in this study were reported only in patients treated with intravenous diphenhydramine.

From a clinical practice standpoint, intravenous diphenhydramine has been standard treatment for acute urticaria when an intravenous treatment is required,[5] either used alone for moderate or mild cases or as an adjunct therapy with other medications for severe cases such as

Table 5. Summary of adverse events by system organ class and preferred term.

Adverse events	IV Diphenhydramine 50 mg (n=135)	IV Cetirizine 10 mg (n=127)
Patients with ≥1 adverse event, No. (%)	18 (13.3)	5 (3.9)
Nervous system disorders, No. (%)	10 (7.4)	3 (2.4)
Dizziness	6 (4.4)	0
Burning sensation	2 (1.5)	0
Dysgeusia	1 (0.7)	1 (0.8)
Headache	1 (0.7)	1 (0.8)
Paresthesia	0	1 (0.8)
Presyncope	0	1 (0.8)
Gastrointestinal disorders, No. (%)	4 (3.0)	1 (0.8)
Nausea	4 (3.0)	0
Dyspepsia	0	1 (0.8)
Vomiting	1 (0.7)	0
General disorders and administration site conditions, No. (%)	3 (2.2)	1 (0.8)
Pyrexia	2 (1.5)	0
Warm sensation	0	1 (0.8)
Injection site pain	1 (0.7)	0
Skin and subcutaneous tissue disorders, No. (%)	3 (2.2)	1 (0.8)
Urticaria	2 (1.5)	0
Erythema	1 (0.7)	0
Hyperhidrosis	0	1 (0.8)
Pruritus	1 (0.7)	0
Cardiac disorders, No. (%)	1 (0.7)	0
Bradycardia	1 (0.7)	0
Immune system disorders, No. (%)	1 (0.7)	0
Anaphylactic reaction	1 (0.7)	0

Safety population.

anaphylaxis. However, use of diphenhydramine has known disadvantages in emergency medicine, in which crowding and patient throughput represent important issues.[19] Given the sedating effects of diphenhydramine, discharging patients from EDs after they receive the medication carries potential risk to patient and public safety, leading some to recommend that patients not drive a car for a period after treatment.[11,12] One study found that patients compromised by a first-generation antihistamine were unaware of their reduced ability to function, based on impaired performance measures.[9] This may place patients in legal jeopardy because certain states have laws in place that prohibit driving under the influence of any drug such as diphenhydramine that impairs function.[20] Additionally, because of its anticholinergic and sedation adverse effects, use of diphenhydramine is discouraged in the 2019 American Geriatrics Society Beers Criteria for potentially inappropriate medication use in older adults, with recognition that acute use for severe allergic reactions may be appropriate because there are no alternatives.[21] In a 2000 to 2006 National Hospital Ambulatory Medical Care Survey study involving elderly patients (≥65 years) and using previous yet similar Beers criteria, diphenhydramine accounted for 1.17% of ED visits in the cohort.[22] In our study, 9 patients per arm were aged 65 years or older (representing 7% of the study population), with no significant difference in the primary outcome between the study treatments in this small cohort of elderly patients. In addition, no overall differences in sedation and overall safety were observed between patients aged 65 years or older versus younger patients. Overall, these clinical trial data have applicability for emergency medicine as well as other settings, including emerging models of care in which safety and sedation will be of paramount importance.

Although economic outcomes were not captured in the current clinical trial, the observed reductions of time spent in ED, ED readmission rate, and rescue medication use with intravenous cetirizine may confer cost savings.

Because the use of first-generation oral antihistamines has markedly decreased with the availability of second-generation agents owing to both efficacy and safety considerations across many conditions that include chronic urticaria and allergic rhinitis, the introduction of intravenous cetirizine may allow similar advancement in the treatment of acute urticaria throughout the health care system.

In conclusion, this study demonstrated that intravenous cetirizine (10 mg) is as effective as intravenous diphenhydramine (50 mg) in the treatment of acute urticaria while offering benefits that include less sedation and a lower overall adverse event rate, as well as less time spent at the treatment center and a lower rate of return to the facility.

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