Review of H_1 Antihistamines in the Treatment of Chronic Idiopathic Urticaria

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GOAL

To understand chronic idiopathic urticaria (CIU) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the effect of CIU on patient quality of life.
2. Discuss antihistamine use in the treatment of CIU.
3. Explain the anti-inflammatory properties of antihistamines.

CME Test on page 104.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: July 2005.

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Dr. Monroe is in the speakers program and has been a clinical investigator for Sanofi-Aventis and Schering-Plough Corporation. The author discusses off-label use for antihistamines, antileukotrienes, corticosteroids, cyclosporine, doxepin, and tricyclic antidepressants. Dr. Fisher reports no conflict of interest.

Chronic idiopathic urticaria (CIU) can have a profound effect on patient quality of life (QOL). Ideally, any therapy used to treat CIU should be effective across a wide range of doses without causing unwanted side effects; a wide therapeutic window allows the physician to tailor treatment to the individual. Oral H_1 antihistamines are the mainstay of therapy for CIU, but agents within this class diverge in their individual therapeutic indices. The literature was reviewed to compare the currently available oral H_1 antihistamines regarding their efficacy and safety at a wide range of doses. If sedation and cognitive impairment are considered relevant to treatment selection due to their effect on QOL and safety, then newer-generation agents should be selected over older-generation antihistamines. There are few well-controlled clinical studies in which newer-generation agents have been directly

Accepted for publication April 12, 2005.

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compared. Moreover, there are no evidence-based data demonstrating statistical superiority of one newer-generation agent over another in the treatment of CIU. However, of the newer agents, those that are labelled nonsedating *at recommended doses (fexofenadine, loratadine, and desloratadine) should be selected over cetirizine. In cases where the physician judges that a higher-than-recommended dose should be prescribed, or when the patient is likely to take a higher dose, the relative safety profile of these agents demands detailed consideration.*

Cutis. 2005;76:118–126.

How idiopathic is chronic idiopathic urticaria (CIU)? With the fast pace of scientific and medical discovery, it is anomalous that diseases with no known cause remain. However, despite the fact that CIU is less well understood than many other diseases, recent findings have partially illuminated this condition's etiology.

At least 2 subgroups of patients with CIU exist. One group is composed of 30% to 50% of patients with CIU with autoimmune chronic urticaria caused by autoantibodies against either the high-affinity immunoglobulin E (IgE) receptor FcεRI or, less commonly, IgE.[1,2] Patients in this subgroup have an increased likelihood of thyroid autoimmunity; thyroid autoantibodies, Hashimoto thyroiditis, and Graves disease are recognized as being associated with CIU.[3] Indeed, 27% of patients with CIU have high-titre antithyroglobulin, antithyroid peroxidase autoantibodies, or both, and 19% have abnormal thyroid function.[3] However, the remaining 50% to 70% of patients with CIU are truly idiopathic, because there is no known cause for the disease.[1]

In keeping with the illusive nature of CIU, the prevalence of the disease has not been firmly established.[4] Most recent estimates suggest that 15% to 20% of the US population experience at least one episode of urticaria in their lifetime, and up to 3% of the population are diagnosed with CIU.[5,6] Interestingly, middle-aged women are more likely to experience the condition than other groups[7]; also, women are approximately 3 times more likely than men to acquire any autoimmune disease during their lifetime,[8] supporting the notion that CIU is often an autoimmune disease.

Quality of Life

The impact of a disease extends beyond physical signs and symptoms; health-related quality of life (QOL) also should play a pivotal role in the evaluation of the effect of a disease or its treatment. This parameter is particularly pertinent to CIU, as evidenced by O'Donnell et al[9] whose analysis of a disease-specific, purpose-designed questionnaire and the Nottingham Health Profile demonstrated that patients with chronic urticaria experienced considerable disability, handicap, and reduced QOL. Part 1 of the health profile showed that patients were restricted in areas of mobility, sleep, and energy and experienced pain, social isolation, and altered emotional reactions. Part 2 showed that patients experienced problems in relation to work, home management, social life, relationships, sex life, hobbies, and holidays. Interestingly, patients in this survey had almost identical scores for part 1 of the health profile as did patients with coronary artery disease; both groups experienced lack of energy, feelings of social isolation, and emotional upset.[9]

Perhaps because skin diseases are so visible and thus potentially stigmatizing, dermatology patients can be impacted significantly in terms of QOL; however, the effect of CIU appears to be particularly acute. Using the validated Dermatology Life Quality Index (DLQI), a survey of 170 consecutive patients had results that showed that patients with CIU experienced greater QOL impairment than outpatients with either psoriasis, acne, or vitiligo and experienced a comparable level of impairment to patients with severe atopic dermatitis.[10] Because of CIU's devastating effect on health-related QOL and the discomfort of CIU, appropriate treatment selection is crucial. The ideal treatment for CIU would not only rid the patient of the wheals, edema, and pruritus that characterize the condition but also improve QOL. This review outlines the treatment options available, focusing on oral H_1 antihistamines, and offers a means of differentiating this class of agent.

Antihistamines in the Treatment of CIU

It is well established that elevated tissue levels of histamine are found in the skin of patients with different forms of chronic urticaria.[11-13] Although more subclasses of histamine receptors have been identified, those initially isolated—H_1 and H_2—are involved in the cutaneous responses seen in urticaria. Specifically, the binding of histamine to the H_1 receptor causes erythema (by vasodilation), edema (by increasing vascular permeability), and itching. The same responses, with the exception of itching, are caused by histamine binding to the H_2 receptor. In 30% to 50% of patients diagnosed with CIU, histamine release from mast cells leads to wheal formation because of an autoimmune process.

In contrast, patients with CIU without this autoimmune response experience the same effects of mast cell degranulation and subsequent release of histamine by a process yet to be elucidated.

The sentinel involvement of histamine in CIU is, therefore, unequivocal; irrespective of etiology, the appropriate use of H_1 antihistamines—which stabilize an active conformation of the H_1 receptor and thus prevent activation by histamine—remains the basis of treatment.[14] However, for patients unresponsive to conventional H_1-antihistamine monotherapy, adjunctive treatments often are prescribed including a combination of H_1 antihistamines (either 2 different newer-generation agents concurrently or a newer-generation agent plus a first-generation agent at night), H_2 antihistamines, tricyclic antidepressants (principally doxepin), antileukotriene therapy, and intermittent pulses of corticosteroids.[15] In the event of inadequate symptom control after these therapies have been explored, immunomodulatory agents such as cyclosporine have been used to treat patients refractory to conventional therapy.[14]

The method of activity for the adjunctive treatments is based on the following approaches: blocking H_1 and H_2 receptors, blocking nonhistamine mediators of urticaria, and blocking the cellular and inflammatory components of the urticarial reaction. In summary, because H_1 antihistamines are first-line therapy for CIU, and for many patients remain the only option available, the selection of the optimal antihistamine is of vital importance.

Selection of Antihistamines

The first antihistamine was developed in 1937; in the 1940s, phenbenzamine became the first commercially available antihistamine, followed by similar H_1-receptor antagonists such as chlorpheniramine, brompheniramine, and diphenhydramine. Despite its relative antiquity, diphenhydramine remains the most widely used antihistamine in the United States.[16] These first-generation H_1-receptor antagonists, though effective in the treatment of urticaria and allergic rhinitis, were shown to cause undesired side effects for 2 distinct reasons: their lack of selectivity for the H_1 receptor and their propensity to cross the blood-brain barrier and affect the central nervous system.[17]

As a result of their lack of selectivity, older-generation agents cause anticholinergic effects such as dry mouth, headache, and urinary retention.[18-20] Furthermore, at supraclinical doses, some antihistamines are toxic[16] and have been shown to cause sinus tachycardia.[21] Children have been known to experience severe toxic reactions and even death following overdose of older-generation antihistamines because of the drug's lack of selectivity.[22-25]

Because older-generation antihistamines can bind to H_1 receptors in the brain and histamine in the brain plays a role in central nervous system arousal and alertness, these agents also are associated with sedation and cognitive impairment (eg, impaired sensorimotor coordination and decreases in attention span, memory function, ability to process information, and psychomotor performance[16,26,27]). The binding of first-generation antihistamines to cerebral H_1 receptors has been demonstrated in many studies employing objective psychometric tests and also by the relatively new technique of positron emission tomographic imaging.[28-30]

Newer-Generation Antihistamines

Newer-generation antihistamines were developed in the early 1980s with the aim of being more specific for the H_1 receptor, as well as of overcoming the adverse events observed with older agents. As testament to achieving this goal, allergists agree that newer-generation antihistamines are preferred to first-generation agents because of their more favorable efficacy:safety ratio.[16,18] Although there is no such formal consensus among dermatologists and those specifically treating CIU, it is likely the same logic would apply if equivalent efficacy between old and new antihistamines can be established for CIU. This review explores the newer-generation antihistamines available in the United States for the treatment of CIU: fexofenadine, loratadine, desloratadine, and cetirizine. An evidence-based analysis of the efficacy of these agents and an analysis of the therapeutic window of these antihistamines, with particular focus on their sedation and cognitive impairment potential, are emphasized (Table).

Efficacy of Newer-Generation Antihistamines

Numerous randomized double-blind clinical studies have demonstrated the efficacy of fexofenadine,[31-34] loratadine,[35,36] desloratadine,[37,38] and cetirizine[39,40] in relieving the symptoms of CIU.

Fexofenadine—The safety and efficacy of various doses of fexofenadine at relieving the symptoms of CIU has been established in several large randomized controlled clinical trials. Two similar CIU studies investigated the efficacy of fexofenadine HCl using doses of 20, 60, 120, and 240 mg twice daily (BID). In both studies, doses of 60 mg or more BID were shown to reduce severity of pruritus, number of wheals, and interference with sleep and normal daily activities compared with placebo.[33,34] Furthermore, studies in Japanese and Thai patients have indicated that the effectiveness

H_1 Antihistamines in Chronic Idiopathic Urticaria: Efficacy and Safety Comparison*

Antihistamine	Efficacy	Anticholinergic Effect	Drowsiness (Recommended Dose)	Drowsiness (> Recommended Dose)	Impairment (Recommended Dose)	Impairment (> Recommended Dose)
Cetirizine	3	0	1	1	1	1
Chlorpheniramine	2/3	3	2	3	2	3
Desloratadine	3	0	0	1	0	1
Diphenhydramine	3	3	3	3	3	3
Fexofenadine	3	0	0	0	0	0
Hydroxyzine	3	3	3	3	3	3
Loratadine	3	0	0	1	0	1

*0 indicates none; 1, mild; 2, moderate; 3, strong.

of fexofenadine 60 mg BID is not limited by ethnicity or genotype.[41,42]

Although many studies have examined some QOL parameters as secondary endpoints as a component of efficacy studies, fexofenadine has been studied using the validated DLQI and Work Productivity and Activity Impairment questionnaires.[43] Two identically designed 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials examined the effects of 60 mg BID on patients aged 12 to 65 years with moderate to severe CIU. Fexofenadine treatment significantly improved overall DLQI score compared with placebo ($P \leq .0002$), and also significantly increased work productivity ($P \leq .014$). In addition, a trend toward increased classroom productivity and significant improvements in 5 of the 6 individual DLQI domains were observed.[43]

The efficacy and safety of a range of once-daily (QD) doses of fexofenadine have been evaluated in a large, multicenter, double-blind, placebo-controlled, parallel-group, dose-ranging study.[31] Adults (N=222) were randomized to receive either fexofenadine HCl 60, 120, 180, or 240 mg QD or placebo QD for 6 weeks. The combined fexofenadine groups showed a significant reduction in mean total symptom score (pruritus score and number of wheals) compared with placebo ($P=.0019$). The study suggested that 180 mg QD is the optimal dose for the treatment of CIU because this dose alone significantly reduced the number of wheals compared with placebo ($P=.0064$) and significantly improved mean total symptom score consistently over the 6-week study period ($P<.05$).[31] Supporting the efficacy of this once-daily dose, a recent double-blind placebo-controlled study of fexofenadine HCl 180 mg QD was shown to produce a beneficial effect on urticaria.[32]

Loratadine—The relative efficacy of loratadine and the first-generation antihistamine hydroxyzine has been established in a large 4-week (optional 12-week) trial comparing the 2 compounds with placebo in 172 patients with CIU. Patients were randomized to receive either: 10 mg loratadine QD and placebo BID; hydroxyzine 3 times daily; or placebo 3 times daily. As measured by all efficacy evaluations (physician and patient evaluations of the effect of treatment at each visit plus patient daily diary cards), loratadine and hydroxyzine were found to be more effective than placebo and clinically comparable to each other.[35]

In the only placebo-controlled comparative study between 2 newer-generation antihistamines in the treatment of CIU, Guerra et al[44] showed that loratadine was more effective than cetirizine in some aspects of controlling the symptoms of CIU. In this double-blind study, 116 patients with CIU were randomly assigned loratadine 10 mg, cetirizine 10 mg, or placebo QD for 28 days. Both active drugs significantly reduced global clinical symptoms ($P<.05$), but loratadine was more rapid in developing its activity than cetirizine ($P<.01$ at day 3) and also appeared to be safer when the frequency of treatment-emergent side effects were compared.[44]

Desloratadine—Desloratadine is the major active metabolite of loratadine, which has been available in the United States since 2002 for the treatment of CIU. The efficacy of the drug has been evaluated in 2 major randomized controlled clinical trials.[37,38]

Ring et al[37] reported that desloratadine exhibited superior efficacy compared with placebo in a multicenter, randomized, double-blind trial of 190 patients with a history of CIU. Patients were assigned to receive either desloratadine 5 mg QD or placebo QD for 6 weeks. The active treatment was superior to placebo at reducing pruritus and overall symptoms after the first dose and throughout the 6-week study.[37] Similarly, therapeutic response and global CIU status, as well as QOL measures such as interference with sleep, were improved with desloratadine compared with placebo throughout the study period.[37] Using the same dose (5 mg QD), a further 6-week placebo-controlled study of desloratadine indicated the effectiveness of this agent at relieving CIU symptoms.[38] Over the study period, the mean total CIU symptom score was significantly improved compared with placebo, as were the individual scores of pruritus, number of hives, and the size of the largest hive. Interference with sleep was reduced and performance of daily activities was improved with desloratadine. These statistically and clinically significant improvements were seen within the first 24 hours of treatment and were sustained throughout the 6-week treatment period.[38]

Cetirizine—As with loratadine, cetirizine has been shown to be as effective as first-generation hydroxyzine at relieving the symptoms of CIU.[40] For example, a 4-week, multicenter, randomized, double-blind, double-dummy trial investigated the efficacy and safety of cetirizine 10 mg QD and hydroxyzine 25 mg 3 times daily compared with placebo in patients with CIU. Patients in the cetirizine and hydroxyzine groups showed significant reductions during weeks 1, 2, 3, and 4 in the number and size of lesions and in the severity of pruritus compared with patients who received placebo. In addition, physician and patient evaluations at the end of week 4 revealed an improvement in urticarial symptoms for the cetirizine and hydroxyzine groups compared with the placebo group.[40]

All 4 newer-generation H_1 antihistamines (fexofenadine, loratadine, desloratadine, and cetirizine) have been shown to be superior to placebo at treating the symptoms of CIU, and both loratadine and cetirizine have been proven to be as effective as first-generation hydroxyzine.[35,40] Although no trials have evaluated fexofenadine and desloratadine compared with hydroxyzine, comparisons demonstrating equivalence have been made with their parent compounds (loratadine[35] and terfenadine[45]).

There are few controlled studies in which newer-generation antihistamines have been directly compared, and there is no evidence-based data demonstrating statistical superiority of one second-generation agent over another in the treatment of CIU. For example, although a recent trial compared the efficacy of cetirizine with fexofenadine, the results are weakened by the study design. Patients with CIU were randomized to either cetirizine 10 mg (n=52) or fexofenadine 180 mg (n=45); at 28 days, 51.9% (27) and 4.4% (2) of cetirizine and fexofenadine patients, respectively, were symptom free (P=.00001), while partial improvement was experienced by 36.5% (19) of cetirizine patients and 42.2% (19) of fexofenadine patients.[46] However, there was no control group, baseline symptom severity data were not provided, and the authors did not describe how the patients' symptoms were assessed.[46] Therefore, a definitive assessment of the relative efficacy of newer-generation antihistamines cannot be achieved by reviewing published trials alone.

Anti-inflammatory Properties

Due to the absence of well-designed placebo-controlled comparisons of newer-generation antihistamines, other properties have been examined to aid treatment comparisons. For example, it has been suggested that some H_1-receptor antagonists may achieve anti-inflammatory effects in a clinical context, which could prove advantageous in the treatment of CIU because the disease is characterized by tissue inflammation.[47]

To investigate the anti-inflammatory activity of fexofenadine, an immunohistochemical evaluation of the agent was undertaken in patients with CIU.[48] Twenty patients received fexofenadine HCl 180 mg QD for 4 weeks; the expression of adhesion molecules, mast cell proteases, and proinflammatory cytokines were evaluated before and after treatment, as were the patients' assessments of urticarial symptoms. After treatment with fexofenadine, significant decreases in the expression of endothelial leukocyte adhesion molecule-1 (P=.02), vascular cell adhesion molecule-1 (P=.04), and tryptase (P=.04) were observed, confirming the hypothesis that fexofenadine has some anti-inflammatory properties.

This study in humans must be put into context with the numerous in vitro, ex vivo, and animal studies that have been conducted in this area. A review of such data suggests that all newer-generation antihistamines inhibit the release or generation of multiple inflammatory mediators, including IL-4,

IL-6, IL-8, IL-13, prostaglandin D_3, leukotriene C, tryptase, histamine, and the tumor necrosis factor α–induced chemokine regulated upon activation normal T cell expressed and secreted, in addition to eosinophil chemotaxis and adhesion molecules.[47] For example, both loratadine and desloratadine (10 μmol/L) significantly inhibited the expression of intercellular adhesion molecule-1 and class II HLA antigen (HLA-DE) in nasal epithelial cells in vitro.[49] However, many of these anti-inflammatory effects have only been observed at high drug concentrations.[47] For example, an in vitro study of cetirizine assessing the inhibition of IL-5–dependent eosinophil survival revealed a concentration of 100 μmol/L was required to achieve significant inhibition—much higher than that used clinically.[47,50]

Clearly, if clinical anti-inflammatory effects necessitate doses higher than those recommended for allergic diseases, drugs that can be used at higher doses without causing unwanted side effects such as sedation and cognitive impairment may be of the greatest utility in the treatment of CIU. This is a particularly pertinent point because patients with CIU may be prescribed much higher doses than recommended to manage symptoms effectively.[17]

The Therapeutic Window—Because of the lack of rigorously designed clinical trials comparing the efficacy of second-generation antihistamines and the putative anti-inflammatory activities of these agents that may occur at higher-than-recommended dosing levels, the relative safety of agents may direct the selection of the optimum antihistamine for the treatment of CIU. Ideally, an agent would be effective at a wide range of doses without causing unwanted side effects. This is because a wide therapeutic window permits the physician to optimize treatment to the individual. The safety of the newer-generation antihistamines has been assessed in numerous clinical trials, usually as secondary analyses to efficacy parameters; indeed, all of the efficacy studies described here indicated a good safety and tolerability profile for each of the antihistamines.

Clinical trials, however, do not always reflect the reality of clinical practice. Patients taking antihistamines frequently overcomply with their medication,[51] particularly if they do not experience immediate relief. Furthermore, as previously mentioned, it is occasionally necessary for dermatologists to prescribe high doses of antihistamines for patients who do not respond to standard-dose first-line therapy.[17] Thus, it is valid to examine the safety of the different antihistamines at high doses to obtain a true picture of how drugs may be affecting patients.

Sedation and Impairment—A number of studies using objective psychometric tests have indicated that newer-generation antihistamines generally have better sedative profiles than first-generation agents; however, at higher doses, sedation and impairment become evident.

Two meta-analyses of published data on antihistamines report that newer drugs had lower impairment/nonimpairment ratios than older agents.[28,29] That is, proportionally more studies indicated nonimpairment versus impairment with the newer agents compared with their predecessors. However, the same meta-analyses revealed that both loratadine and cetirizine were associated with sedation/impairment in a number of tests, often when they were used at higher-than-recommended doses. In contrast, fexofenadine, even at doses of up to 360 mg, was not associated with any sedation or impairment and had an impairment:nonimpairment ratio of zero.[28,29]

A study by Mann et al[52] corroborates the finding that different newer-generation antihistamines have the potential to cause sedation, with fexofenadine being the least likely of those studied to do so. This prescription-event monitoring study showed that the odds ratios for the incidence of sedation were 0.63 for fexofenadine and 5.53 for cetirizine compared with loratadine.[52] Higher-than-recommended doses of loratadine[53] and desloratadine[54] also can cause sedation.

A recent approach to the question of blood-brain barrier penetration involves the use of positron emission tomography. This technique has been used to study the binding of antihistamines to cerebral H_1 receptors. Tashiro et al[30] used positron emission tomographic imaging to compare fexofenadine with cetirizine by examining relative H_1 receptor occupancy in the brain. Quantitative analysis showed that fexofenadine did not occupy H_1 receptors in the cerebral cortex, while cetirizine occupied between 20% to 50% of the H_1 receptors, depending on the brain region.[30] These findings support evidence from comparative trials that indicate that although cetirizine is less sedating than older antihistamines, it causes more sedation and impairment of performance than other second-generation antihistamines. As a result, the US Food and Drug Administration has classified cetirizine as sedating rather than nonsedating, and the product carries the full sedation precaution.

Comment

Antihistamines can be used effectively to control the symptoms of CIU; newer-generation antihistamines have been shown to be as effective as

their predecessors at relieving patients of their symptoms[35,40] and improving their QOL.[43] However, there is a paucity of well-designed placebo-controlled comparative clinical trials; the data available indicate that agents are effective and safe, but they do not provide a means to assess which agent is the safest and most effective. Instead, we must examine alternative sources of evidence to help us select the optimum antihistamine for the treatment of CIU.

Evidence from pharmacologic studies indicates that newer agents demonstrate some anti-inflammatory activity, which could provide additional therapeutic benefit. However, these studies have largely been limited to in vitro tests and animal modeling and do not yet provide the means to differentiate agents.

Newer-generation antihistamines vary in their propensity to cause sedation and cognitive impairment, with cetirizine representing the most impairing of the class, as recognized by its sedating description by the US Food and Drug Administration. At recommended doses, fexofenadine, loratadine, and desloratadine have not been found to cause significant impairment and are labeled as nonsedating by the US Food and Drug Administration. However, patients with urticaria are known to take above-recommended doses[51] and physicians occasionally prescribe off-label doses to achieve the desired level of symptom control. The risk of sedation caused by these 2 factors should be considered in practice when selecting an antihistamine.

Sedation and impairment affect QOL and manifest as decreased classroom learning ability and decreased work productivity.[28] Furthermore, it has been suggested that cerebral H_1-receptor blockade is associated with falls in the elderly and cognitive slowing, and is a contributing factor in traffic accidents.[27]

Conclusion

In controlled clinical studies of CIU, the second-generation H_1-antihistamines have been proven to be clinically comparable to the most potent of the first-generation antihistamines, such as hydroxyzine. Clinical studies comparing these agents are few and have shown no statistically significant differences in efficacy.

If sedation and cognitive impairment are to be considered relevant to the choice of therapy for CIU because of their impact on QOL and safety, then newer-generation agents should be selected over older-generation antihistamines.[37,40] Furthermore, of the new agents, those that are labeled nonsedating at recommended doses (fexofenadine, loratadine, and desloratadine) should be selected over cetirizine. However, in cases where the physician judges that a higher-than-recommended dose should be prescribed or when the patient is likely to take a higher dose, fexofenadine should be considered. In addition to its proven efficacy in treating the symptoms of CIU,[31,33,34] fexofenadine is the only antihistamine that is nonsedating, even at doses 2 to 4 times above the recommended levels.

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