

Pharmacology and therapeutics

Levocetirizine and rupatadine in chronic idiopathic urticaria

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Abstract

Background Chronic idiopathic urticaria (CIU) is a common dermatological condition. Its pathogenesis involves mainly histamine and also other mediators, including platelet-activating factor (PAF) and tumor necrosis factor- α (TNF- α). In the absence of an exact etiology, H₁-antihistaminics are the mainstay of treatment. Levocetirizine is widely prescribed for CIU. Rupatadine, a newer antihistaminic, has PAF receptor antagonist activity and has shown anti-TNF- α activity *in vitro*. These additional anti-inflammatory effects may improve its efficacy.

Objectives This study was conducted to compare the efficacy and safety of rupatadine and levocetirizine, respectively, in CIU patients.

Methods A prospective, open, comparative, randomized study was conducted in 100 patients, of whom 50 were treated with levocetirizine and 50 were treated with rupatadine. Efficacy parameters used were urticarial activity score (UAS) and Dermatology Life Quality Index (DLQI) values. Safety was evaluated by monitoring for adverse drug reactions and by using the critical flicker fusion threshold (CFFT) test and a visual analog scale (VAS) at baseline, and at 2, 4, and 6 weeks.

Results The mean UAS decreased to 0.10 in the levocetirizine group and to 0.38 in the rupatadine group. Patients in the levocetirizine group showed a more significant ($P < 0.001$) improvement, although symptoms improved in both groups. Significant reductions in mean DLQI scores were observed in both groups, but the decrease was statistically significant in the levocetirizine group ($P < 0.05$). Somnolence was the most common side effect in both groups. Patients in the levocetirizine group showed more psychomotor impairment based on the CFFT test. Findings on the VAS showed sedative effects in both groups ($P < 0.05$).

Conclusions Levocetirizine was found to be more efficacious than rupatadine in CIU patients, but both drugs caused mild sedation.

Introduction

Chronic idiopathic urticaria (CIU) is defined as the occurrence of daily, or almost daily, wheals and itching for at least six weeks with no identifiable cause. The lifetime prevalence in the general population is 0.5%.¹ A higher incidence is seen in adults, and the condition affects women more commonly than men.² Some authors have suggested that mediators such as histamine, platelet-activating factor (PAF), tumor necrosis factor- α (TNF- α), interleukin-8 (IL-8), leukotriene-4 (LT-4), and others may be involved in the pathogenesis of CIU.³

As the etiology of CIU is largely unknown, its treatment is focused mainly on achieving symptomatic relief. H₁-antihistaminics, principally second-generation drugs, are the mainstay of therapy.⁴ Response rates vary from

44% to 91% in different studies.⁵ Many other drugs such as mycophenolate mofetil, montelukast, methotrexate, and immunosuppressive therapy have been tried in the treatment of unresponsive cases. These drugs are subject to their own limitations, such as a slower response rate and higher cost in comparison with standard treatment with antihistaminics.⁶

Levocetirizine is a widely prescribed H₁-antihistaminic for CIU patients.⁷ Rupatadine is a newer second-generation antihistaminic that is used for allergic rhinitis. It has dual antagonistic activity against histamine and PAF receptors.⁸ It has also shown anti-TNF- α activity *in vitro*.⁹ Therefore, rupatadine has broader anti-inflammatory properties, which may increase its effectiveness in CIU patients. Studies have been conducted using rupatadine for allergic rhinitis in European countries, but data

on its use in CIU are limited. Hence, we conducted this study to compare the efficacy and safety of rupatadine and levocetirizine, respectively, in CIU.

Materials and methods

This was an open, randomized, comparative study conducted in patients attending an outpatient department of dermatology. The study was approved by this institution's review board. A total of 100 patients were enrolled after they had signed written informed consent.

Study design

Patients were randomly divided into two groups (A and B) using computer-generated random numbers. Group A ($n = 50$) received levocetirizine, and Group B ($n = 50$) received rupatadine. Both drugs were given at a dosage of 10 mg once per day for six weeks. Patients were followed at 2-week intervals up to six weeks. Baseline investigations including a complete blood count and routine urine and stool analyses were conducted in all patients to exclude some causes of urticaria.

Study population

Patients of both genders aged 12–65 years were included. Potential subjects who were excluded from the study included: pregnant and lactating women; patients with acute urticaria; women taking oral contraceptives; patients taking drugs such as corticosteroids, nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors within two weeks of the study start date; patients who were hypersensitive to rupatadine or other antihistaminics; patients with urticarial vasculitis, autoimmune urticaria, physical urticaria, kidney disorders, or liver disorders; patients taking drugs that affect psychomotor function; and patients taking erythromycin or ketoconazole.

Evaluation

Efficacy was assessed using an urticarial activity score (UAS),⁴ the critical flicker fusion threshold (CFFT) test,¹⁰ and the Dermatology Life Quality Index (DLQI).¹¹ Safety was assessed using a visual analog scale (VAS)¹² and observations of adverse drug reactions. The UAS is derived from the sum of wheals and pruritus scores, which were measured at every visit. The total score ranges from 0 to 6, where 0 is the minimum and 6 is the maximum score.

The CFFT test has been widely used as an aid to measure psychomotor impairment.¹⁰ Responses were determined according to the mean of three ascending and three descending frequencies of flicker at every visit. Three sets of each measurement were performed, and the mean of all six readings was used in the analysis.

The DLQI was used to evaluate quality of life in patients at baseline and at the end of six weeks.¹¹ A 10-cm long VAS

anchored at the endpoints of “wide awake” and “nearly asleep” was used to measure the level of daytime sedation at every visit.¹² Safety was evaluated according to spontaneously reported as well as checklist-based monitoring of adverse drug reactions.

Statistical analysis

Results were expressed as the mean $\pm$ standard error (SE) of the mean. Analysis was performed using Student's *t*-test. A paired *t*-test was used within the groups. An unpaired *t*-test was used to compare results between the two groups. A *P*-value of < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows Version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

Both groups were comparable for demographic characteristics including patient age and gender. As Table 1 shows, in the levocetirizine group, the mean wheals score was 2.76 at baseline and decreased to 0.88 at two weeks, 0.18 at four weeks, and significantly declined to 0.10 at six weeks ($P < 0.001$). In comparison, in the rupatadine group, the mean score for wheals began at 2.84 at baseline and reduced to 0.34 at week 6. Similarly, the mean score for pruritus in the levocetirizine group was 2.56 at baseline and reduced to 0.00 at week 6, whereas that in the rupatadine group was 2.46 at baseline and reduced to

Table 1 Urticarial activity scores in patients with chronic idiopathic urticaria treated with levocetirizine (Group A; $n = 50$) or rupatadine (Group B; $n = 50$)

UAS	Group A Mean $\pm$ SE	Group B Mean $\pm$ SE
Wheal score		
Baseline	2.76 $\pm$ 0.06	2.84 $\pm$ 0.52
2 weeks	0.88 $\pm$ 0.06 ^a	1.40 $\pm$ 0.08 ^a
4 weeks	0.18 $\pm$ 0.05 ^a	0.66 $\pm$ 0.08 ^a
6 weeks	0.10 $\pm$ 0.04 ^a	0.34 $\pm$ 0.07 ^a
Pruritus score		
Baseline	2.56 $\pm$ 0.09	2.46 $\pm$ 0.09
2 weeks	0.60 $\pm$ 0.09 ^a	1.04 $\pm$ 0.08 ^a
4 weeks	0.12 $\pm$ 0.04 ^a	0.40 $\pm$ 0.07 ^a
6 weeks	0.00 $\pm$ 0.00 ^a	0.16 $\pm$ 0.06 ^a
Total score		
Baseline	5.32 $\pm$ 0.12	5.30 $\pm$ 0.11
2 weeks	1.46 $\pm$ 0.16 ^{ab}	2.44 $\pm$ 0.14 ^a
4 weeks	0.32 $\pm$ 0.08 ^{ab}	1.00 $\pm$ 0.14 ^a
6 weeks	0.10 $\pm$ 0.04 ^{ab}	0.38 $\pm$ 0.08 ^a

UAS, urticarial activity score; SE, standard error.

^a $P < 0.05$ (statistically significant) for difference with baseline values.

^b $P < 0.05$ (statistically significant) for difference with Group B.

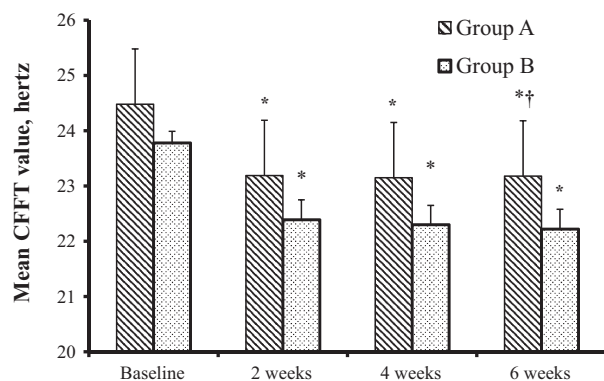


Figure 1 Critical flicker fusion threshold (CFFT) test findings in patients with chronic idiopathic urticaria treated with levocetirizine (Group A) or rupatadine (Group B). * $P < 0.05$ for difference with baseline values; † $P < 0.05$ for difference with Group B

0.16 at week 6. Although both groups showed a statistically significant reduction, the levocetirizine group showed a more significant ($P < 0.001$) improvement in symptom scores at every follow-up time-point than did the rupatadine group.

Figure 1 indicates that the mean CFFT value in the levocetirizine group was 24.40 at baseline and declined to 23.18 at six weeks. In the rupatadine group, CFFT values were 23.74 at baseline and 22.22 at six weeks. Statistical analysis showed that patients treated with levocetirizine demonstrated greater psychomotor impairment than those treated with rupatadine.

At the baseline visit, the mean DLQI score in the levocetirizine group was 11.92, which diminished to 2.04 at week 6. In the rupatadine group, the mean DLQI score at baseline was 10.66 and decreased to 2.32 ($P = 0.05$) at the end of treatment. Although there was a statistically significant decrease in DLQI scores in both groups, that in the levocetirizine group indicated greater improvement (Fig. 2).

The VAS values increased in both groups. This indicates that both treatment groups experienced a degree of sedation that was statistically significant ($P < 0.05$). However, there was no difference between the two groups. Somnolence was the most common side effect reported by patients in both treatment groups: 16% of patients in the rupatadine group and 10% of patients in the levocetirizine group reported somnolence. Only one patient in the rupatadine group complained of asthenia. No significant difference was seen between the two treatment groups in the incidence of adverse effects.

Discussion

The majority of patients in the present study were aged > 30 years, which makes the study population comparable

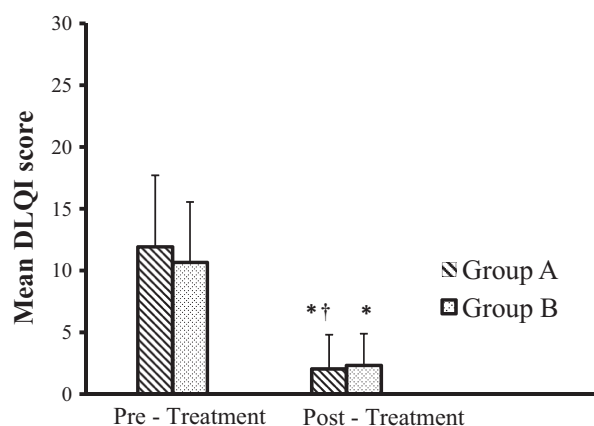


Figure 2 Comparison of Dermatological Life Quality Index (DLQI) findings in patients with chronic idiopathic urticaria treated with levocetirizine (Group A) or rupatadine (Group B). * $P < 0.05$ for difference with pretreatment indices; † $P < 0.05$ for difference with Group B

with those of earlier studies.^{13–15} In this study, a higher incidence of CIU was found in female subjects, which also corresponds with previous studies.^{13,14} An earlier study which used levocetirizine for the treatment of CIU reported a 79% reduction in wheals,¹³ whereas we found a 96.3% reduction in our levocetirizine-treated group. The greater wheal reduction identified in the present study in comparison with that found in the earlier study¹³ may reflect our use of a higher dose of levocetirizine. Some authors suggest that a higher dose of non-sedating antihistaminic should be used in patients who do not respond to conventional doses.¹⁶

In another study, levocetirizine was compared with desloratadine in 886 CIU patients over a treatment period of four weeks. Levocetirizine decreased pruritus scores significantly in the first week and over the entire treatment period.¹⁷ Similar improvements in pruritus scores were noted in the present study.

The pathogenesis of CIU is still not well understood. It is assumed that mast cell activation initiates the inflammatory process in CIU and that various inflammatory mediators are involved, including neutrophils, eosinophils, IL, PAF, and TNF- α . A few studies have demonstrated that some mediators of mast cells upregulate the expression on endothelial cells of adhesion molecules for leukocytes, which is an important component of the late-phase allergic response. Endothelial activation leads to increased expression of endothelial adhesion molecules such as intercellular adhesion molecules-1 (ICAM-1) and vascular adhesion molecules-1 (VCAM-1). Another study mentioned the roles of endothelial leukocyte adhesion molecules-1 (ELAM-1) and P-selectin in the inflammation of

chronic urticaria.¹⁸ Epithelial activation is associated with the generation and release of a number of chemokines, such as RANTES (regulated on activation, normal T cell expressed and secreted), macrophages inflammatory protein-1 (MIP-1), monocyte chemotactic protein-1 (MCP-1), IL-8 and eotaxin, which are chemoattractants for eosinophils, mast cells, lymphocytes, neutrophils, and basophils.¹⁹ Previous research has shown increased expression of TNF- α and IL-3 on endothelial cells and has detected perivascular cells in the upper dermis of patients with CIU, as well as increased IL-4, IL-6, IL-1 β , and IL-12 p70, in comparison with healthy controls.²⁰

The present study found a higher reduction in the total symptom score in the levocetirizine group than in the rupatadine group. This effect of levocetirizine may derive from its additional anti-inflammatory properties because levocetirizine 5 mg treatment has been shown to have twice the affinity for the H₁ receptor as cetirizine. Caproni *et al.* reported the anti-inflammatory effects of levocetirizine in patients with CIU by demonstrating a significant decrease in serum levels of ELAM-1 and P-selectin, which may reflect inhibitory activity against the rolling and extravasation of neutrophils towards inflamed skin.¹⁸

Similarly, it has been demonstrated that levocetirizine inhibits eotaxin, IL-1, TNF- α , and VCAM-1 production in endothelial cells by blocking the transcriptional complex NF- κ B.²⁰ This mechanism may be responsible for its anti-inflammatory effects in a manner similar to that demonstrated in other uses of antihistamines.

Additionally, previous research identified increased mRNA expression on tumor necrosis factor receptor (TNFR), interferon- γ (IFN- γ), IL-10 receptor (IL-10R), cysteine chemokine receptor 3 (CCR₃), cysteine chemokine receptor 6 (CCR₆), and decreased TLR₂ mRNA expression in the peripheral blood mononuclear cells of CIU patients.²¹ These factors may play a role or roles in the pathogenesis of CIU, but the issue requires further research.²¹

A study conducted by Park and colleagues reported that the activation of human nasal epithelial cells by TLR (especially TLR₃) may trigger an inflammatory process.²² This may be inhibited by levocetirizine through the suppression of the toll-IL-1 receptor (TIR) domain containing adapter inducing IFN- β (TRIF) and receptor-interacting protein (RIP).²²

Another study in which levocetirizine was compared with loratadine in 60 CIU patients also concluded that levocetirizine reduced total symptom scores more significantly than loratadine.¹⁵ Some studies have shown levocetirizine to have additional anti-inflammatory properties.²² Thus, more studies are required to explore its extra anti-inflammatory effects.

Gimenez-Arnau *et al.* carried out a placebo-controlled study in CIU using two doses of rupatadine of, respectively, 10 mg and 20 mg.²³ They demonstrated a significant effect in patients treated with the 20-mg dose in comparison with those treated with 10 mg or placebo.²³

A single blinded research study in which rupatadine and levocetirizine were compared in CIU patients reported that rupatadine was better than levocetirizine in terms of the clinical improvement and absolute reduction in eosinophil count achieved.²⁴ In the present study, improvement was noticed based on UAS in both groups, although the levocetirizine group showed a greater improvement. Both treatment groups showed an improved quality of life. A greater reduction in DLQI scores was observed in the levocetirizine group. This suggests that antihistaminics not only relieve symptoms but also improve quality of life in CIU patients.

A different study in which repeated doses of levocetirizine were given for five days did not produce psychomotor impairment evaluated using the CFFT test in healthy volunteers in comparison with a placebo-treated control group.²⁵ In comparison with this earlier study,²⁵ significant decreases in CFFT values were seen at all follow-up visits in our levocetirizine group. The slight impairment of psychomotor function as reflected by CFFT scores may reflect the regular use of levocetirizine for six weeks.

A study in which rupatadine at different single doses (10 mg, 20 mg, 40 mg and 80 mg) was compared with a 25-mg dose of hydroxyzine and placebo found decreases in CFFT values at doses of 40 mg and 80 mg but no psychomotor impairment at doses of 10 mg and 20 mg of rupatadine.²⁶ These earlier findings²⁶ are contradictory to the findings of the present study. However, we used rupatadine continuously for six weeks, which may have resulted in the impairment of psychomotor function.

Another study concluded that levocetirizine did not show sedative effects in comparison with diphenhydramine using a VAS.²⁵ The present study showed a statistically significant difference in the levocetirizine group in comparison with baseline data, which is contradictory to the outcomes reported earlier.²⁵

The most common side effect reported by patients in our study was somnolence, which was also reported by patients in other studies.^{15,17} Headache was also commonly reported by levocetirizine-treated patients in previous work.¹⁵ None of our patients reported having headache. One patient in the rupatadine group complained of asthenia. A previous study found asthenia in 11.7% and 10.7% of patients taking rupatadine at doses of 20 mg and 10 mg, respectively, for seasonal allergic rhinitis.²⁷

Chronic idiopathic urticaria is not an allergic condition but a chronic inflammatory disease.²⁸ Drugs that target many inflammatory mediators may show increased effi-

cacy and improve the condition of CIU patients. In a German study, 27.4% of dermatologists and physicians surveyed reported low levels of satisfaction with current options for treating chronic spontaneous urticaria.²⁹ Further studies on antihistaminics are required to explore the broad spectrum anti-inflammatory effects of these drugs. Such investigations may find ways of increasing efficacy and causing fewer adverse drug reactions, which will be helpful in CIU patients. Although the literature suggests that rupatadine has properties additional to those of an H₁-antihistaminic, the present study did not find rupatadine to be superior to levocetirizine.

To conclude, the present study found levocetirizine to be more efficacious than the newer drug rupatadine but both to have equal sedative effects in CIU patients.

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