

The Efficacy of a Two-Fold Increase of H1-Antihistamine in the Treatment of Chronic Urticaria - the Vietnamese Experience

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Abstract

Citation: Tran Thi H, Pham Thi L, Van TN, Thi Minh PP, Nguyen Trong H, Chau Van T, Nguyen Huu S, Trinh Minh T, Dinh Huu N, Hoang Van T, Tran Cam V, Le Huyen M, Tran Hau K, Gandolfi M, Satolli F, Feliciani C, Tirant M, Vojvodic A, Lotti T. The Efficacy of a Two-Fold Increase of H1-Antihistamine in the Treatment of Chronic Urticaria - the Vietnamese Experience. Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2019.069>

Keywords: Chronic urticaria; Chronic idiopathic urticaria; Antihistamine; Fexofenadine; Levocetirizine

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Received: 02-Jan-2019; **Revised:** 16-Jan-2019; **Accepted:** 17-Jan-2019; **Online first:** 28-Jan-2019

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

BACKGROUND: Chronic urticaria, a mast cell-driven condition, is common, debilitating and hard to treat. H1-antihistamines are the first line treatment of chronic urticaria, but often patients do not get satisfactory relief with the recommended dose. European guidelines recommend increased antihistamine doses up to four-fold.

AIM: We conducted this study to evaluate the efficacy of increased H1-antihistamine doses up to two-fold in Vietnamese chronic urticaria patients.

METHODS: One hundred and two patients with chronic urticaria were recruited for treatment with levocetirizine (n = 52) or fexofenadine (n = 50). Treatment started at the conventional daily dose of 5 mg levocetirizine or 180 mg fexofenadine for 2 weeks and then increased to 10 mg levocetirizine or 360 mg fexofenadine for 2 weeks if patients did not have an improvement in symptoms. At week 0, week 2 and week 4 wheal, pruritus, size of the wheal, total symptom scores, and associated side-effects were assessed.

RESULTS: With the conventional dose, the total symptom scores after week 2 decreased significantly in both groups compared to baseline figures, i.e. 7.4 vs 2.3 for levocetirizine group and 8.0 vs 2.6 for fexofenadine group (p < 0.05). However, there were still 26 patients in each group who did not have improvements. Of these 26 patients, after having a two-fold increase of the conventional dose, 11.5% and 38.5% became symptom-free at week 4 in levocetirizine group and fexofenadine group, respectively. At week 4 in both groups, the total symptom scores had significantly decreased when compared with those at week 2 (2.8 ± 1.5 versus 4.7 ± 1.6 in levocetirizine group; 2.1 ± 1.9 versus 5.1 ± 1.4 in fexofenadine group). In both groups, there was no difference in the rate of negative side effects between the conventional dose and the double dose.

CONCLUSION: This study showed that increasing the dosages of levocetirizine and fexofenadine by two-fold improved chronic urticaria symptoms without increasing the rate of negative side effects.

Introduction

Urticaria is an allergic reaction of the skin capillaries to many endogenous or exogenous allergens. This disease can be characterised by the formation of wheals, angioedema or both and can disappear within 24 hours [1]. Patients with urticaria often experience a sensation of itching or burning which can interfere with daily life. Based on chronology, urticaria is divided into acute and chronic.

As opposed to acute urticaria, chronic urticaria is defined by recurrent episodes occurring at least twice a week for 6 weeks, possibly lasting for many months, or many years [2], [3], [4]. Urticaria is also classified as spontaneous and inducible with and without any specific eliciting factor involved. Chronic urticaria substantially impacts on a patient's quality of life with an effect on both physical and mental health. Studies have shown that health status scores in chronic spontaneous urticaria patients are comparable to those with coronary artery disease [5].

The exact cause of urticaria is unknown, but there are some factors contributing to the development of the disease. In urticaria, mast cells are activated, release histamine and other mediators, which result in vasodilatation, inflammatory recruitment cells, as well as sensory nerve activation. The therapeutic approach to chronic urticaria involves the identification and elimination of its underlying causes, the avoidance of eliciting factors, tolerance induction, and/or the use of pharmacological treatment to prevent mast cell mediator release and/or the effects of mast cell mediators [1]. The main option in therapies aimed at symptomatic relief is to reduce the effect of mast cell mediators such as histamine and others on the target organs. Many symptoms of urticaria are mediated primarily by the actions of histamine on H₁-receptors located on endothelial cells (the wheal) and sensory nerves (neurogenic flare and pruritus). Thus, continuous treatment with H₁-antihistamines is of eminent importance in the treatment of urticaria. It is supported not only by the results of clinical trials but also by the mechanism of action of these medications [6], [7].

There have been some studies on the effectiveness of antihistamine and other drugs in the treatment of chronic urticaria with varying results. Mainstay therapeutics are antihistamines, which in chronic urticaria, shows poor response rates when used in standard dosage. The up-dosing of antihistamines to four-fold does improve the response rate [8], [1]. In Vietnam, conventional doses of H₁-antihistamine are widely used in the treatment of chronic urticaria, and in practice, the majority of patients have a good response to conventional doses. However, difficult-to-treat chronic urticaria patients remain a challenge and data on doses used for Vietnamese patients is scarce.

We conducted this study to evaluate the efficacy and safety of a two-fold increase of H₁-antihistamine (fexofenadine and levocetirizine) in the treatment of chronic urticaria.

Methods

From March to August 2013 we recruited 102 patients with chronic urticaria, aged 12 years and above at the National Hospital of Dermato-venereology. Exclusion criteria were: (1) urticaria with glottis oedema or accompanied by diarrhoea; (2) physical urticarial; (3) presence of other diseases such as liver, kidney, endocrine, psychiatric or systemic disease; (4) pregnant and lactating women; (5) women taking contraceptive drugs; (6) patients who had taken antihistamines or steroids in the past 2 weeks; (7) the use of any other drugs during the treatment period; (8) patients with biochemical abnormalities. Biochemistry was tested at week 0 and

week 4 including urea, creatinine, glucose, liver enzymes, cholesterol, and triglycerides.

One hundred and two patients with chronic urticaria were randomly recruited into 2 groups: 1) levocetirizine group (52 patients) and 2) fexofenadine group (50 patients). Treatment started at the conventional dose in each group. 5 mg levocetirizine daily for the levocetirizine group and 180 mg fexofenadine daily for the fexofenadine group. After 2 weeks if the symptoms were persistent, the patients were given a double dose.

The patients underwent clinical examinations. Each of the following symptoms was scored according to the Urticaria Activity Score (UAS) 4 [9] at week 0, week 2 and week 4.

Pruritus score: none: 0 points; mild: 1 point (present but not annoying or troublesome); moderate: 2 points (troublesome but did not interfere with sleep); severe: 3 points (severe pruritus, which is troublesome enough to interfere with normal daily activities or sleep)

Wheal score: none: 0 points; 1-19 wheals/24 hours: 1 point; 20-50 wheals/24 hours: 2 points; more than 50 wheals/24 hours or large confluent areas of wheals: 3 points.

We also scored the size of the biggest wheal as following: none: 0 points; less than 1.25 cm in diameter: 1 point; 1.25-2.5 cm in diameter: 2 points; more than 2.5 cm in diameter: 3 points.

Total symptom score: 0 points: free of symptoms; 1-3 points: mild; 4-6 points: moderate; 7-9 points: severe.

This study used SPSS statistical software (version 16.0) with the use of a t-test for quantitative variables and a χ^2 test for qualitative variables.

This study was approved by the hospital ethics board of National Hospital of Dermatology and Venereology in 2013. The investigator ensured that the study was conducted by the Declaration of Helsinki.

Results

The background characteristics of patients in the two groups were not significantly different as shown in Table 1.

The mean age of our patients was 36.2 years (aged 14-65) for the levocetirizine group and 39 years (aged 12-68) for the fexofenadine group. None of the patients was at a mild level at week 0. There were 69.2% female patients in the levocetirizine group and 64% in the fexofenadine group. The majority of patients (73.2% in levocetirizine group and 46% in

fexofenadine group) had suffered from urticaria from 6 weeks to 1 year.

Table 1: The background characteristics of the patients

	Levocetirizine group (n = 52)	Fexofenadine group (n = 50)
Age		
Mean	36.2 ± 0.5	39 ± 0.7
Range	14-65	12-68
≤ 20	7 (13.5%)	10 (20%)
21-40	29 (55.8%)	25 (50%)
41-60	14 (26.9%)	14 (28%)
≥ 61	2 (3.8%)	1 (2%)
Sex		
Male	16 (30.8%)	18 (36%)
Female	36 (69.2%)	32 (64%)
The duration of disease		
6 week-1 year	32 (73.2%)	23 (46.0%)
1-5 years	16 (30.8%)	14 (28.0%)
> 5 year	4 (7.7%)	13 (26.0%)

At week 0, total symptom scores were 7.4 ± 1.3 in the levocetirizine group and 8.0 ± 1.0 in the fexofenadine group. At week 2 (2 weeks after treatment with a conventional dose) the total symptom scores 2.3 ± 2.6 and 2.6 ± 2.8 respectively as shown in Table 2 had decreased significantly when compared with those at week 0.

Table 2: The symptom scores of the two group treated with a conventional dose at week 0 and week 2

	Levocetirizine (n = 52)		p	Fexofenadine (n = 50)		p
	Week 0	Week 2		Week 0	Week 2	
Pruritus	2.7 ± 0.8	0.9 ± 0.9	< 0.05	2.9 ± 0.2	1.0 ± 1.1	< 0.05
Wheal	2.2 ± 0.6	0.8 ± 0.9	< 0.05	2.5 ± 0.7	0.9 ± 0.9	< 0.05
Size of wheal	2.7 ± 0.5	0.7 ± 0.9	< 0.05	2.5 ± 0.7	0.8 ± 0.9	< 0.05
Total symptom score	7.4 ± 1.3	2.3 ± 2.6	< 0.05	8.0 ± 1.0	2.6 ± 2.8	< 0.05

However, at this point, there were still 26 patients in each group who were still not symptom-free. Their total symptom scores were 4.7 ± 1.6 in the levocetirizine group and 5.1 ± 1.4 in the fexofenadine group (p > 0.05) as shown in Table 3. These patients were treated with a double dose for 2 weeks. The patients who had recovered maintained their conventional daily dose and left our trial.

At week 4, we evaluated the remaining 26 patients who were treated with a double dose in each group. The result showed that total symptom scores were significantly reduced (Table 3).

Table 3: The symptom scores of the two groups treated with a double dose at week 2 and week 4

	Levocetirizine (n = 26)		p	Fexofenadine (n = 26)		p
	Week 2	Week 4		Week 2	Week 4	
Pruritus	1.7 ± 0.6	0.9 ± 0.7	< 0.05	1.9 ± 0.7	0.7 ± 0.9	< 0.05
Wheal	1.5 ± 0.8	1.0 ± 0.7	< 0.05	1.7 ± 0.6	0.7 ± 0.6	< 0.05
Size of wheal	1.4 ± 0.7	0.9 ± 0.4	< 0.05	1.5 ± 0.7	0.7 ± 0.6	< 0.05
Total symptom score	4.7 ± 1.6	2.8 ± 1.5	< 0.05	5.1 ± 1.4	2.1 ± 1.9	< 0.05

With 2.8 ± 1.5 in the levocetirizine group and 2.1 ± 1.9 in the fexofenadine group. Between the two groups, there was no statistically significant difference (p > 0.05). In the levocetirizine group at week 4, 11.5% of the patients had a resolution of symptoms, 61.5% with a mild form of the disease, 26.9% moderate and no patient was severe. In the fexofenadine group at week 38.5% of patients had a

resolution of symptoms, the proportion of patients with a mild level was 26.9% (versus 23.0% before treatment), and a moderate level was 34.6% (versus 57.8% before treatment). There was no patient with a severe form of the disease at week 4 (versus 19.2% before treatment) as shown in Figure 1.

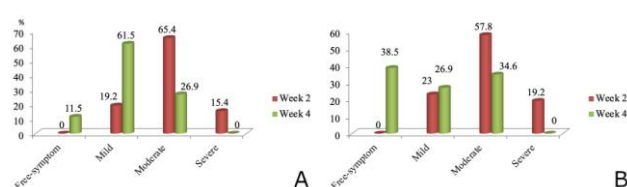


Figure 1: Severity of disease in the two groups at week 2 and week 4; A) Levocetirizine group; B) Fexofenadine group

The proportion of undesirable side effects at a conventional dose of the levocetirizine group was 9.6% and for the fexofenadine group 8.0%. When the dose was doubled the proportions of side effects were 11.5% and 10.2% respectively for the two groups. Overall the most common side effects were drowsiness and fatigue. Results concluded that no patients had any biochemical abnormalities after 4 weeks of treatment (at least with the level of urea, creatinine and liver enzymes).

Discussion

This study of H₁-antihistamines doses of 102 patients with chronic urticaria provided three important results. H₁-antihistamine at a conventional dose affected recovery in about half of the patients. In the remaining difficult-to-treat patients a two-fold dose of H₁- antihistamines improved symptoms of urticaria significantly. This study also found that levocetirizine seemed to be slightly more effective than fexofenadine, though this didn't prove to be statistically significant.

H₁-antihistamine affected improving the symptoms of all chronic urticaria patients. More than half of the patients recovered from all symptoms on 5 mg levocetirizine or 180 mg fexofenadine per day. These patients continued to maintain this therapy for a long period after the trial. Though many patients still had symptoms after 2 weeks of treatment with a conventional dose. Pre-treatment, most had suffered from the disease for over 6 months, and the severity of urticaria was moderate to severe (results not shown).

Given that histamine mediates almost all symptoms of urticaria through H₁-receptors located on nerves and endothelial cells, the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF)

guidelines recommend that the first line of treatment should be with non-sedating H₁-antihistamine [10]. Trials support the use of these drugs in most forms of urticaria [10] however in a study of 390 patients, only about 44% responded well to this treatment: 29% were discharged asymptomatic with another 15% only showing a partial relief of symptoms [11]. This raises some questions as to the need for an increased dose of H₁-antihistamine also whether individual patients respond better to one antihistamine over another [12].

A two-fold increase in the dose of histamine H₁ reduced the symptoms in patients not responding to conventional doses. General concerns over increasing the dose are the negative side effects associated with the drug. However, this study found that side effects were not different between a conventional dose and an increased dose. Overall the most common side effects were drowsiness and fatigue. Second-generation H₁-antihistamines (such as levocetirizine and fexofenadine) represent a substantial therapeutic advance and often show a lack of cardiotoxicity, an absence of cholinergic side effects and display minimal sedation [12]. Increasing the dose of antihistamines is a good solution in difficult-to-treat urticaria, replacing the need to switch to other drugs such as systemic corticosteroids. With an increased dose of both levocetirizine and fexofenadine, there was a significant improvement in the quality of life of the patient.

European guidelines allow a four-fold increase to the normal dose of H₁-antihistamines [1] however as there are no published studies in Vietnam on an increased dose we increased the dose only 2 times as a precaution. After 2 weeks of double dose therapy, there were still many long-term and severe patients who were still not fully asymptomatic. From the fifth week, these patients were treated with alternative antihistamines before attempting other drugs such as montelukast, cyclosporin and systemic corticosteroid. The Staevska et al., (2010) study of 80 patients with difficult-to-treat urticaria showed that the 25 patients who failed to respond to 20 mg desloratadine, 7 became symptom-free on 20 mg levocetirizine [12]. As mentioned, in previous studies of urticaria other proinflammatory mediators such as interleukine-4 and leukotriene may contribute to clinical and histological images of the disease [13]. Mast and basophilic cells of volunteers without urticaria were incubated with serum from idiopathic chronic urticarial patients and produced interleukine-4 and leukotriene. These two mediators can cause perivascular infiltration of the inflammatory cells that affect skin cells. This infiltration creates the difference between a histological lesion of acute urticaria and that of physical urticaria. The use of antihistamines cannot cure all the symptoms of urticaria however several clinical trials using montelukast, in combination with antihistamines (cetirizine, fexofenadine, loratadine or desloratadine) revealed better results than those using antihistamines alone

(improving symptoms and the quality of life). Interestingly, when used as a standalone treatment, monotherapy leukotriene antagonists have no effect on chronic urticaria [13].

Levocetirizine and fexofenadine have been known to have an equal effect in improving the symptoms of chronic urticaria. However, in this trial at week 4, the rate of symptomatic relief was higher in the levocetirizine group than in the fexofenadine group. Different H₁-antihistamines may have different effects in the treatment of urticaria. In a study of 886 patients, results revealed that levocetirizine 5 mg was significantly more efficacious than desloratadine 5 mg in the treatment of chronic urticaria [14]. Though it must be noted that fexofenadine is less dependent on liver function so it can be prescribed to patients with hepatic diseases.

Of course, there were some limitations to be noted in this study. Firstly, the effectiveness was evaluated based on clinical improvement, which can often be subjective between investigators and patients. Secondly, the study's duration was only 4 weeks; a long-term follow-up study is lacking thus far. Finally, UAS was used to evaluate the severity of chronic urticaria on the day in which the patients checked into the hospital, UAS7 was not used (which evaluates the last seven days). USA7 is clearly more precise than UAS but this information was not available at the time and therefore could not be used in this study.

References

1. Wiley J, Sons A. EAACI/GA2LEN/EDF/WAO guideline: management of urticaria. *Allergy*, 64, 1427-1443. Zuberbier T. et al. (2018). The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2009; 73(7):1393-1414.
2. Asero R. Chronic idiopathic urticaria: a family study. *Annals of Allergy, Asthma & Immunology*. 2002; 89(2):195-6. [https://doi.org/10.1016/S1081-1206\(10\)61937-0](https://doi.org/10.1016/S1081-1206(10)61937-0)
3. Fusari A, Colangelo C, Bonifazi F, Antonicelli L. The autologous serum skin test in the follow-up of patients with chronic urticaria. *Allergy*. 2005; 60(2):256-8. <https://doi.org/10.1111/j.1398-9995.2005.00673.x> PMID:15647050
4. Mahesh PA, Kushalappa PA, Holla AD, et al. House dust mite sensitivity is a factor in chronic urticaria. *J Investig Allergol Clin Immunol*. 2004; 14(1):50-54.
5. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *British Journal of Dermatology*. 1997; 136(2):197-201. <https://doi.org/10.1111/j.1365-2133.1997.tb14895.x> PMID:9068731
6. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life. *Allergy*. 2009; 64(4):605-12. <https://doi.org/10.1111/j.1398-9995.2008.01913.x> PMID:19133920
7. Weller K, Ardelean E, Scholz E, Martus P, Zuberbier T, Maurer M. Can on-demand non-sedating antihistamines improve urticaria symptoms? A double-blind, randomized, single-dose study. *Acta*

- dermato-venereologica. 2013; 93(2):168-74. <https://doi.org/10.2340/00015555-1434> PMID:23053062
8. Chow SK. Management of chronic urticaria in Asia: 2010 AADV consensus guidelines. *Asia Pacific Allergy*. 2012; 2(2):149-60. <https://doi.org/10.5415/apallergy.2012.2.2.149> PMID:22701866 PMCID:PMC3345329
9. Godse KV. Urticaria meter. *Indian J Dermatol*. 2012; 57(5):410-411. <https://doi.org/10.4103/0019-5154.100510> PMID:23112370 PMCID:PMC3482813
10. Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM, Kapp A, Kozel MM, Maurer M, Merk HF, Schäfer T. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy*. 2006; 61(3):321-31. <https://doi.org/10.1111/j.1398-9995.2005.00962.x> PMID:16436141
11. Humphreys FF, Hunter JA. The characteristic of urticaria in 390 patients. *Br J Dermatol*. 1998 ; 138:635-8. <https://doi.org/10.1046/j.1365-2133.1998.02175.x>
12. Staevska M., Popov T., Kralimarkova T, et al. The effectiveness of antihistamines in up to four-times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010; 125:676-82. <https://doi.org/10.1016/j.jaci.2009.11.047> PMID:20226302
13. Jáuregui I, Ferrer M, Montoro J, Dávila I, Bartra J, del Cuvillo A, Moll J, Sastre J, Valero A. Antihistamines in the treatment of chronic urticaria. *J Investig Allergol Clin Immunol*. 2007; 17(Suppl 2):41-52. PMID:18228682
14. Potter PC, Kapp A, Maurer M, Guillet G, Jian AM, Hauptmann P, Finlay AY. Comparison of the efficacy of levocetirizine 5 mg and desloratadine 5 mg in chronic idiopathic urticaria patients. *Allergy*. 2009; 64(4):596-604. <https://doi.org/10.1111/j.1398-9995.2008.01893.x> PMID:19053988