

# Treatment of Recalcitrant Chronic Urticaria With Nonsedating Antihistamines: Is There Evidence for Updosing?

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## ■ Abstract

Nonsedating antihistamines are the first-choice treatment for all forms of urticaria. In patients with recalcitrant urticaria who do not respond to conventional doses of antihistamines, current guidelines recommend increasing doses by up to 4 times in order to obtain better control of the disease. Although few studies have been conducted, there are convincing data from controlled trials for cetirizine, levocetirizine, and desloratadine that support the use of increased doses of such drugs in unresponsive patients. The use of higher doses of antihistamines has not been associated with increased adverse effects or somnolence. More studies with other second-generation antihistamines are required in order to improve the treatment of patients with severe, recalcitrant urticaria.

**Key words:** Antihistamines. Cetirizine. Desloratadine. Fexofenadine. Levocetirizine. Rupatadine. Urticaria.

## ■ Resumen

Los antihistamínicos no sedantes constituyen el tratamiento de primera elección para todas las formas de urticaria. En pacientes con urticaria recalcitrante que no responden a dosis convencionales de antihistamínicos los lineamientos actuales recomiendan el incremento de la dosis hasta 4 veces hasta obtener un mejor control de la enfermedad. Aunque el número de investigaciones es reducido, existen datos convincentes de estudios controlados para cetirizina, levocetirizina y desloratadina que sustentan el uso de dosis superiores en pacientes no respondedores. Se ha observado que la utilización de mayores dosis de antihistamínicos no se asocia con un incremento de la frecuencia de efectos adversos o de somnolencia. Se requieren estudios adicionales con otros antihistamínicos de segunda generación para mejorar el tratamiento de los pacientes que presentan urticaria severa recalcitrante.

**Palabras clave:** Antihistamínicos. Cetirizina. Desloratadina. Fexofenadina. Levocetirizina. Rupatadina. Urticaria.

## 1. Introduction

Current international guidelines propose that second-generation (nonsedating) antihistamines constitute the first line of treatment for all forms of urticaria, whether acute or chronic. Nonsedating antihistamines have been shown to have a long therapeutic half-life, with other major advantages over first-generation antihistamines, such as a lack of cardiotoxicity, an absence of cholinergic side effects, and minimal sedation. However, it has been reported that all second-generation H<sub>1</sub>-antihistamines may cause a small degree of sedation [1].

In 1 study of 390 patients with urticaria who were treated with anti-H<sub>1</sub> antihistamines, 44% responded well, 29% became asymptomatic, and 15% showed partial improvement [2]. These results suggest that a substantial number of patients,

especially those with chronic urticaria, do not show satisfactory responses to this first line of therapy.

In patients who do not respond to approved doses of antihistamines it is currently advised to progressively increase the conventional dose by up to 4 times [3]. This recommendation was initially put forward as an expert opinion-based guideline. The purpose of this paper is to present data obtained in recent investigations supporting the use of increased doses of second-generation antihistamines in patients with urticaria who do not respond adequately to conventional doses. We will present relevant studies performed with each of the different second-generation antihistamines, and draw conclusions regarding this therapeutic strategy based on the information available.

It is important to mention that controlled clinical trials on

the efficacy of different drugs used for the treatment of urticaria are generally confounded by the presence of notable placebo effects. For example, in 1 study, placebo was associated with a reduction of over 75% in mean pruritus scores, mean number of wheals, and mean urticaria activity scores in 21%, 12% and 14% of patients, respectively [4].

#### *Cetirizine Studies*

Zuberbier et al [5] administered cetirizine 20 mg daily (twice the conventional dose) or placebo for 3 weeks to 11 patients with cholinergic urticaria. Cetirizine induced a significant reduction in wheals, erythema, pruritus, and global symptom scores. The investigators concluded that cetirizine at twice its normally recommended dose is highly efficient in patients with cholinergic urticaria [5]. Similar results were obtained in another open study of 21 patients with chronic idiopathic urticaria (CIU) reported by Kameyoshi et al [6]. Nevertheless, Asero [7] reported an increase in efficacy in only a small number of patients who received 30 mg of cetirizine, which is 3 times the recommended dose. He suggested that few patients with severe CIU obtain better control with high doses of antihistamines, and that most patients with severe disease eventually have to undergo more aggressive treatment with anti-inflammatory or immunomodulatory drugs [7].

#### *Fexofenadine Studies*

Two studies have suggested that increasing the dose of fexofenadine from 60 mg to 240 mg twice daily does not increase control of urticaria symptoms. Finn et al [8] performed a 4-week, multicenter, double-blind, placebo-controlled study in 439 patients with CIU. The doses of fexofenadine were 20, 60, 120, or 240 mg twice a day. Efficacy results were similar in the 60-, 120-, and 240-mg groups, and the reduction in pruritus and number of wheals was greater with these doses than with the 20-mg dose. The authors recommended fexofenadine doses of 60 mg twice a day or greater for the treatment of urticaria, since there appeared to be only a slight additional improvement in treatment effect with twice-daily doses of 120 and 240 mg [8].

Nelson et al [9] treated 418 patients with chronic urticaria with placebo or fexofenadine 20, 60, 120, or 240 mg twice a day in a 4-week, double-blind, randomized, placebo-controlled study. There were greater reductions in urticaria symptoms in the 60-mg group than in the 20-mg group, and similar reductions were observed in the 60-, 120-, and 240-mg groups. The authors concluded that twice-daily doses of 60 mg or higher were the most effective [9].

#### *Desloratadine and Levocetirizine Studies*

Two studies have investigated the effects of increased doses of desloratadine in patients with urticaria. In a prospective, randomized, double-blind study of patients with acquired cold urticaria, Siebenhaar et al [10] administered desloratadine 5 or 20 mg per day for 7 days. They observed that both doses significantly reduced the volume of cold-induced wheals and areas of hyperthermic skin, and also improved the critical temperature threshold (CTT) and the critical stimulation time

threshold (CSTT). Desloratadine 20 mg significantly reduced cold-induced wheal volume, the CTT, and the CSTT as compared with the 5-mg dose. Furthermore, desloratadine at 4 times the standard dose did not increase the rate of somnolence [10]. The authors proposed that increased antihistamine doses might lead to stabilization of mast cells or downregulation of inflammatory signals. Their findings support the current guideline proposal for increased dosing in patients who do not respond to standard antihistamine doses.

Staevska et al [11] treated 80 patients with chronic urticaria in a randomized, double-blind study of levocetirizine or desloratadine. Initially, the conventional daily dose of 5 mg was administered, and doses were increased weekly to 10 mg, or 20 mg if relief of symptoms was unsatisfactory. Patients not responding to 20 mg of one of the antihistamines were switched to 20 mg of the other one. Thirteen patients (9 in the levocetirizine group and 4 in the desloratadine group) became symptom-free at the 5-mg dose and 21 responded to 10 mg (8 to levocetirizine, 7 to desloratadine) and 20 mg (5 to levocetirizine and 1 to desloratadine). Seven out of 28 patients who did not respond to desloratadine 20 mg responded to levocetirizine 20 mg, whereas none of the 18 levocetirizine nonresponders improved with desloratadine 20 mg. Additionally, increased antihistamine doses improved patient quality of life without increasing somnolence. Patients were classified as good responders (15%), nonresponders (10%), and responders to higher doses (75%). The authors concluded that increasing levocetirizine and desloratadine doses by up to 4-fold improved chronic urticaria without affecting safety in approximately three-quarters of patients with difficult-to-treat chronic urticaria [11].

#### *Rupatadine Studies*

Rupatadine is a new second-generation antihistamine with a fast onset of action and higher affinity for the H<sub>1</sub>-receptor than fexofenadine or levocetirizine [12]. This drug has antihistamine and anti-platelet activating factor (PAF) effects. It has been observed that PAF and histamine have mutually complementary activities *in vivo*, and each is able to promote the release of the other [13].

A randomized, double-blind, placebo-controlled study assessed mean pruritus scores in 533 patients with moderate to severe CIU treated with rupatadine 10 or 20 mg once daily for 4 weeks. Reductions in pruritus scores were 57.5% for the 10-mg dose, 63.3% for the 20-mg dose, and 44.9% for placebo. No significant differences between the 2 rupatadine doses were observed [14].

In another randomized, double-blind, placebo-controlled, parallel-group study Dubertret et al [15] investigated the effect of treatment with rupatadine 5, 10, and 20 mg once daily for 4 weeks in patients with moderate to severe CIU. The 10- and 20-mg doses significantly reduced pruritus severity by 62.05% and 71.87%, respectively; the corresponding reduction with placebo was 46.59%. The reductions in total symptom scores were 54.8% for 10 mg, 65.9% for 20 mg, and 38.6% for placebo. The main adverse effects were somnolence (2.9% for placebo, 4.29% for rupatadine 5 mg, 5.41% for 10 mg, and 21.43% for 20 mg) and headache (4.35% for placebo,

2.86% for rupatadine 5 mg, 4.05% for 10 mg, and 4.29% for 20 mg) [15].

Metz et al [16] performed a crossover, double-blind, randomized, placebo-controlled study of 21 patients with acquired cold urticaria who received rupatadine 20 mg daily (the standard dose is 10 mg) or placebo for 1 week. In 11 patients complete responses were obtained, and there were significant improvements in the CSTT and CTT, with reduced scores for wheals, pruritus, burning sensation, and subjective complaints. It was concluded that rupatadine 20 mg given daily to patients with acquired cold urticaria has high efficacy and is well tolerated [16].

The analysis of pooled data from 2 randomized, double-blind, placebo-controlled studies of 538 patients showed that treatment with rupatadine 20 mg daily resulted in a reduction in symptoms of 75% in a higher percentage of patients than treatment with rupatadine 10 mg [4].

## Discussion

An increasing number of controlled studies suggest that increased doses of nonsedating antihistamines increase the proportion of patients obtaining control of urticaria symptoms without inducing higher rates of adverse effects, including somnolence. Some studies have even reported an improvement in quality of life and better sleep related to the reduction in subjective and objective manifestations of urticaria following antihistamine up dosing.

Although few controlled studies have been conducted, it is important to point out that the best results have been achieved with cetirizine, levocetirizine, and desloratadine. In the case of rupatadine, 3 studies showed mixed results and in that of fexofenadine, there was no evidence of a better response to increased doses (Table).

As a consequence, recommendations for up dosing

Table. Studies on Antihistamine Up dosing in Urticaria

Author (Year)	Drug	Study Design	Treatment Duration, wk	No. of Patients	Doses, mg	Improvement With Increased Doses
Zuberbier et al (1996) [5]	Cetirizine	DB, PC Cholinergic urticaria	3	11	20	Good
Kameyoshi et al (2007) [6]	Cetirizine	Open CIU		21	20	Good
Asero (2007) [7]	Cetirizine	Open CIU	2	22	10, 30	Insufficient
Finn et al (1999) [8]	Fexofenadine	DB, PC CIU	4	439	20, 60, 120, 240 twice daily	Similar improvement with 60, 120 and 240 mg twice daily
Nelson et al (2000) [9]	Fexofenadine	DB, PC CIU	4	418	20, 60, 120, 240 twice daily	Similar improvement with 60, 120 and 240 mg twice daily
Siebenhaar et al (2009) [10]	Desloratadine	DB, PC Acquired cold urticaria	1	30	5, 20	Good
Staevska (2010) [11]	Desloratadine Levocetirizine	DB, PC CIU	4	80	5, 10, 20	Good
Giménez-Arnau (2007) [14]	Rupatadine	DB, PC CIU	4	533	10,20	No differences between 10 and 20 mg
Dubertret et al (2007) [15]	Rupatadine	DB, PC CIU	4	277	5, 10, 20	No differences between 10 and 20 mg
Metz et al (2010) [16]	Rupatadine	DB, PC Acquired cold urticaria	1	21	20	Good
Godse (2011)[17]	Ebastine	Open CIU	2	30	10,20	Good

Abbreviations: DB, double-blind; CIU, chronic idiopathic urticaria; PC: placebo-controlled.

in patients with unresponsive urticaria should be viewed cautiously, since only a proportion of patients will respond to increased doses, and favorable results are not uniformly induced by all second-generation antihistamines. In this regard, an important question that should be asked is why antihistamine up dosing is often not effective in urticaria. One possibility that has been proposed is that in vivo receptor occupancy, which takes into account both the affinity of the drug for the receptor and its free plasma concentration, is a far better predictor for human pharmacodynamics and hence antihistamine potency, than in vitro affinity and plasmatic half-life only [18,19].

It should be borne in mind that not all studies are comparable due to the heterogeneity of the populations studied. Most of the studies analyzed included patients with CIU, but some exclusively involved patients with physical urticaria (cold and cholinergic urticaria). More investigations, including studies of new antihistamine molecules such as bilastine, are needed in order to further improve existing therapeutic options for this common and vexing condition.

## Conflicts of Interest

Mario Sánchez-Borges has received honoraria for educational lectures from Laboratorios Leti C.A., Vivax Pharmaceuticals C.A., and Takeda/Nycomed Venezuela. Fernan Caballero-Fonseca has received honoraria for educational lectures from Laboratorios Leti C.A., Vivax Pharmaceuticals C.A., Sanofi-Aventis de Venezuela S.A., and MSD Venezuela.

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■ *Manuscript received September 1, 2012; accepted for publication, December 2, 2012.*

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