ORIGINAL ARTICLE

Effect of Antihistamine Up-Dosing in Chronic Urticaria

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Abstract

Chronic urticaria has an important impact upon patient quality of life, and no treatment has yet been developed capable of effectively controlling the disease. The most recent guidelines recommend the use of non-sedating antihistamines at high doses as second-step therapy before resorting to other treatments. The present review examines the studies published to date on the use of H_1 antihistamines at doses higher than those indicated as therapeutic doses in chronic urticaria. Most of the studies report no significant differences among the studied doses—only a tendency towards increased response on elevating the dose.There are no clinically well designed, randomized double-blind trials comparing efficacy between therapeutic doses and doses higher than those indicated in the corresponding Summary of Product Characteristics. Likewise, there are insufficient data to conduct a meta-analysis and thus classify the degree of evidence of the few available studies, which moreover present contradictory results. At present, the prescription of high-dose H_1 antihistamines is based only on experts opinion. However, considering the high safety profile of these drugs, it would be a good option to evaluate their efficacy at high doses, before moving on to other therapeutic steps.

Key words: Chronic urticaria. Antihistamines. Chronic urticaria treatment.

Resumen

La urticaria crónica es una enfermedad que afecta de una forma importante a la calidad de vida, para la que todavía no contamos con un tratamiento eficaz capaz de controlarla. Las guías más recientes recomiendan emplear antihistamínicos no sedantes a dosis elevadas como segundo escalón terapéutico antes de emplear otros tratamientos.
En esta revisión repasamos los estudios publicados hasta ahora sobre el empleo de antihistamínicos-H_1 a dosis superiores a las indicadas como terapéuticas en urticaria crónica. La mayoría de estudios no encuentran diferencias significativas entre las dosis estudiadas, únicamente una tendencia a incrementar la respuesta al incrementar la dosis. No existen estudios clínicamente bien diseñados y distribuidos aleatoriamente a doble ciego que comparen la eficacia entre dosis terapéuticas con dosis superiores a la indicada en la ficha técnica. Tampoco hay datos suficientes para realizar un meta-análisis y poder clasificar el grado de evidencia de los escasos estudios –con resultados contradictorios- de que se dispone. Por el momento, la prescripción de antihistamínicos H_1 a dosis elevadas se basa únicamente en opinión de los expertos, si bien, por el elevado perfil de seguridad de estos fármacos, será una buena opción, antes de pasar a otros escalones terapéuticos, ensayar la eficacia de dosis altas de antihistamínicos.

Palabras clave: Urticaria crónica. Antihistamínicos. Tratamiento urticaria crónica.

Introduction

H_1 antihistamines [1] are inverse agonists that bind to H_1 receptors, stabilizing the latter in the inactive conformation and therefore interfering with histamine action upon these receptors. Antihistamines are divided into first- and second-generation drugs. The former have been in use since the 1940s and 1950s [2], and are derivatives of muscarinic antagonists, tranquillizers, antipsychotics and antihypertensive agents. The first generation of antihistamine drugs is characterized by low selectivity for the H_1 receptors – as a result of which they induce antimuscarinic, anti-alpha-adrenergic and anti-serotoninergic effects. Their main inconvenience is the fact that they cross the blood-brain barrier. The so-called second-generation antihistamines appeared in the 1980s [3,4], and are characterized by minimum sedation, due to their limited ability to cross the blood-brain barrier, and their high affinity and selectivity for histamine H_1 receptors.

Chronic urticaria is characterized by episodes of pruriginous erythematous-wheal lesions. By definition, the wheals last less than 24 hours, and manifest for at least 6 weeks, during which the episodes occur daily or are present more than twice a week. In 50% of all cases urticaria is associated to angioedema [5].

The calculated prevalence [6] in the Spanish population is 0.65 (95%CI: 0.4-0.8). In 80% of the cases an etiological diagnosis is not established – these presentations being described as idiopathic chronic urticaria. Of the remaining 20%, physical urticarias represent 15% and other types of urticaria 5%.

A Spanish national study [7] on the epidemiological, clinical and socioeconomic factors of allergic diseases showed this disorder represents a strong impact upon patient perceived quality of life, causing many visits to the emergency department and leading to important sick leave from work or diminished school performance. In this context, in relation to the "physical" quality of life subscale of the SF-12 questionnaire, the mean score of the patients with urticaria / angioedema is in percentile 25 of the quality of life score distribution of the Spanish general population, while the mean "mental" quality of life score is under percentile 20.

Despite the morbidity and impact upon patient quality of life [8,9], no treatment to date has been able to fully control the disease. The latest consensus documents and guidelines [10,11] recommend the start of treatment with antihistamines at therapeutic doses, though in the event of insufficient response, they advise a progressive two-, three- or even four-fold increase in the dosage. If the prescription of supratherapeutic doses likewise fails to elicit the desired response, short-course corticosteroids are recommended, and if this does not prove effective, then the only drug to have demonstrated efficacy in one-third of the cases examined in the context of randomized and placebo-controlled trials is cyclosporine [12,13]. On the other hand, very promising results have been published for omalizumab [14-16], despite its high cost [17].

High Doses in Physical Urticarias

All studies published to date reflect a greater response with supratherapeutic antihistamine doses than with the usual doses. Mention should be made to the observations of Siebenhaar et al. [18], who in a randomized, double-blind, three-way cross-over prospective study showed that the administration of 5 and 20 mg of desloratadine significantly increased the tolerance threshold of the cold exposure test. This study found no increase in drowsiness or adverse events with the 20 mg dose of desloratadine.

Previously, in patients with cholinergic urticaria, similar results had been obtained for cetirizine at supratherapeutic doses [19].

However, all these studies are referred to physical urticaria, and the mediator in such cases is histamine and so, it is logical to expect better responses with higher doses of antihistamines.

Chronic Urticaria

In the case of chronic urticaria, the treatment guidelines have agreed to include [11] the possibility of increasing antihistamine doses up to four times with respect to the doses recommended in the Summary of Product Characteristics, if good control is not achieved with the therapeutic doses.

Nevertheless, this recommendation is based on experts opinion, and clinical consensus has not yet been reached, since published results from several studies are contradictory . The first two studies refer to the safety and efficacy of fexofenadine. The first trial, double-blind and group-controlled, was published by Kaplan et al. in 1999 [20], and involved 439 patients with chronic urticaria treated with fexofenadine. The authors observed no increase in response with progressively rising drug doses, for although there were differences between the three highest doses and the lowest dose, no significant differences were recorded among these highest doses. They only found that the three highest doses were superior to the 20 mg dose. The second study, comprising four weeks of treatment, involved a randomized, double-blind and placebo-controlled design, with 418 patients. Improvement in all parameters was recorded with the doses of 20, 60, 120 and 240 mg of fexofenadine. There were differences between the two highest doses versus the 20 mg dose, but not between the rest of the drug doses. Nevertheless, there was a clear tendency towards symptoms improvement when dosage was increased [21].

A third study has been published by Asero et al. [22], involving 22 patients with refractory chronic urticaria failing to respond to therapeutic doses of antihistamines. The patients were administered with rising doses of cetirizine (from 10 to 30 mg), with a responder in only one of the 22 patients.

Bilastine has been studied at different doses in a dose-finding phase II study involving 222 patients with chronic urticaria [23]. This study compared 10, 20 and 30 mg of bilastine, in four parallel groups, versus a placebo control, basing efficacy on the number of wheals and itching. Statistically significant differences were found for all three doses versus placebo, with no differences between doses, though the effect was up-dosing dependent (see Figure). Subsequently, identical results were obtained in the phase III studies. [24].

Lastly, a more recent randomized, double-blind cross-over study [25] has compared the efficacy of levocetirizine

and desloratadine in 80 patients with difficult-to-treat chronic urticaria, administering increasing doses of 5, 10, 15 and 20 mg of both antihistamines if there was poor symptoms control. This study, in contrast to the previous trials, appears to demonstrate that the response is significantly greater to the increase of antihistamine dose. It was found that 13 patients responded to a dose of 5 mg (9 in the levocetirizine group and 4 in the desloratadine group), 15 more responded to 10 mg (8 and 7 in the other groups, respectively), and 6 more to a dose of 20 mg (5 and 1, respectively). However, this still left 18 patients in the levocetirizine group and 25 in the desloratadine group that failed to respond to the highest antihistamine dose (20 mg). Levocetirizine showed significantly better behaviour than desloratadine at all doses, also in relation to patient quality of life. This study offered a secondary finding of great interest, patients did not experience an increase in drowsiness with the up-dosing, and drowsiness even improved in the case of levocetirizine. This appears to support the hypothesis that drowsiness in patients with urticaria is due to interferences with sleep caused by the disease rather than by the use of antihistamines. Furthermore, these results show that with second-generation antihistamines it is possible to establish a good itch and nighttime rest control, being a better option than associating a first-generation antihistamine in a bedtime dose, which in effect would increase drowsiness, particularly taking into account the references of the recent guidelines on the use of first-generation antihistamines [26].

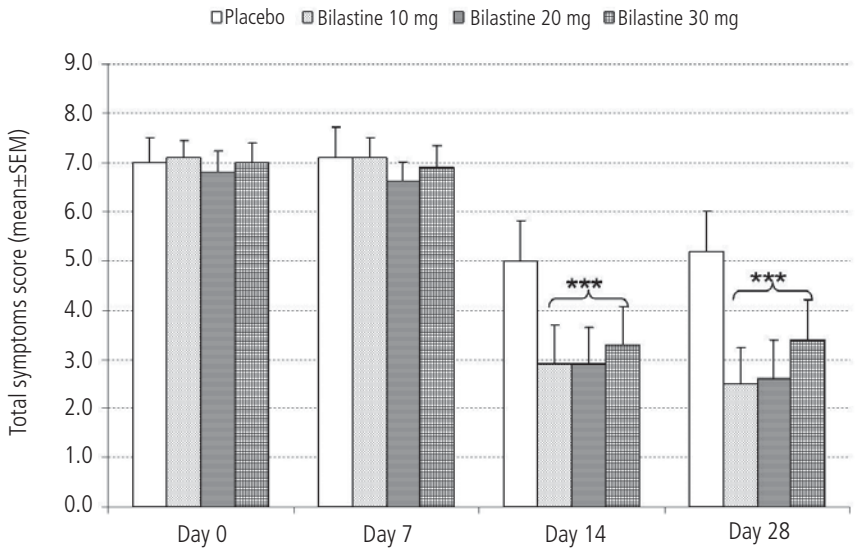

Figure. Dose-finding study (phase II). Evolution of total symptoms score in patients with chronic urticaria treated with bilastine 10, 20 and 30 mg/day.
*** p<0.001 vs placebo.

Another study has been published, though in this case it is an analysis of data accumulated from two randomized trials versus placebo, administering rupatadine [27]. The study concluded that both, the 10 mg and the 20 mg dose, elicit a significantly superior response versus placebo, though with the 20 mg dose a higher number of patients obtained a response of 75% improvement. When examining the studies separately, the first of them [28], a phase II trial comparing doses of 5, 10 and 20 mg, revealed no differences between placebo and the 5 mg dose. No differences were recorded in terms of the number of wheals or in the symptoms scores between the 10 and 20 mg doses, though a clear dose-response effect was observed in favour of the 20 mg dose. The second trial [29] in turn compared the 10 and 20 mg doses, recording no significant differences between them in any of the studied parameters: itching, number of wheals or symptoms scores.

The results are summarized in the Table 1.

The described findings indicate that there is a predominance of studies that record no significant differences between doses, though all of them report a certain dose-response effect in relation to both itching and the number of wheals, as the drug dose is increased. The discrepancy among studies may be due to the antihistamine employed. Due caution is required, however, since there are two studies that include 22 and 80 patients, respectively, versus 857 patients in the studies with fexofenadine, or 222 patients with bilastine.

In sum, a number of studies suggest the possibility of using supratherapeutic doses of antihistamines for controlling chronic urticaria, as agreed by the experts. There are no randomized, double-blind trials comparing efficacy between therapeutic doses and doses higher than those indicated in the corresponding Summary of Product Characteristics. Likewise, there are insufficient data to conduct a meta-analysis and thus classify the degree of evidence of the few available studies, which moreover present contradictory results.

On the other hand, it must be considered that the key factor for antihistaminic activity in treating skin diseases is its distribution at cutaneous level. In this sense, Simons [30] published a very illustrative study comparing three antihistamines (fexofenadine, loratadine and chlorpheniramine), administered at therapeutic doses on a randomized basis, in parallel and with a placebo control group. The study showed the cutaneous concentrations of the three antihistamines differed significantly; that is, the second-generation drugs reached higher levels than the first-generation compound. Likewise, fexofenadine was the most potent antihistamine, reaching higher skin concentrations and with faster action. In the case of the first-generation antihistamine (chlorpheniramine), no detectable skin concentrations were recorded, and its potency in inhibiting histamine-induced wheals was significantly lower. This study evaluated each antihistamine at therapeutic doses, though it would be very interesting to assess the cutaneous distribution in the same way as in the mentioned study, but administering different antihistamine doses, and comparing histamine-induced wheal inhibiting potency in parallel.

It is also important to mention that in daily clinical practice it is not common to increase the antihistamine dosage for treating patients with chronic urticaria. This was reflected

Table 1. Comparison of the included studies

Study	Design	Duration	Antihistamine	No. patients	Dose (mg)	Difference with high doses
Finn AF[20]	Placebo-controlled, randomized, double-blind	4 weeks	Fexofenadine	439	20, 60, 120, 240	No
Nelson HS[21]	Placebo-controlled, randomized, double-blind	4 weeks	Fexofenadine	418	20, 60, 120, 240	No
Asero R[22]	Open, observational	2 weeks	Levocetirizine	22	10, 30	No
Audicana M[24]	Phase II, dose-response, randomized, double-blind, placebo-controlled, parallel	4 weeks	Bilastine	222	10, 20, 30	No
Dubertret L[29]	Phase II, dose-response, randomized, double-blind, placebo-controlled, parallel	4 weeks	Rupatadine	277	5, 10, 20	Yes, between 5 and 10/20, not between 10 and 20
Gimenez-Arnau AM[28]	Randomized, double-blind, placebo-controlled, parallel	4 weeks	Rupatadine	283	10, 20	No
Staevska M[26]	Double blind, randomized, parallel		Levocetirizine and Desloratadine	88	5, 10, 20	Improvement in 2/3 of the patients

in a study of 695 patients [3] on the application of treatment guidelines and the way of treating chronic urticaria, based on questionnaires cumplimented by allergologists and dermatologists. For none of the considered antihistamines did this study find a mean or median dose above the dosage recommended in the corresponding Summary of Product Characteristics. The observed tendency was to add a second drug instead of increasing the antihistamine dose.

Finally, it must be remembered that other mediators, cytokines and chemokines, intervene in chronic urticaria, apart from histamine. In this sense, it has been shown that when incubating healthy mast cells and basophils with sera from patients with chronic urticaria, the cells produced IL-4 and leukotrienes [32]. These mediators could explain the perivascular infiltrates that characterize chronic urticaria [33], since these cytokines and chemokines would attract the mentioned cells towards the skin. The described infiltrate is clearly differentiated from the histopathological lesion corresponding to acute urticaria or physical urticaria; it therefore would be logical for chronic urticaria not to respond only to antihistamines.

In conclusion, it may be stated that while an antihistamine dose increment logically may be expected to elicit symptoms control in histamine - mediated physical urticarias, this point is not clear in the case of chronic urticaria. Studies are therefore needed to clarify this issue. Until then, the above postulate remains a matter of expert opinion only, though the very good safety profile of some second-generation antihistamines could allow the use of doses higher than those specified in the Summary of Product Characteristics. Furthermore, the side effects of the alternative treatments are comparatively more negative. Therefore, before resorting to other therapeutic steps, it always seems to be a good option to test the efficacy of the second-generation antihistamines at supratherapeutic doses, even if on an empirical basis [34].

Conflicts of interest

Joan Bartra Tomás with: UCB, MSD, Dr. Esteve, GSK, Uriach, Schering-Plough, Stallergenes, Allergopharma, Hal Allergy, Leti; Alfonso del Cuvillo Bernal with: UCB, Uriach, MSD, Schering, Alk-Abelló, FAES, Glaxo, Recordati, Almirall, Menarini, Zambon; Ignacio Dávila González with: Allergopharma, ALK-Abelló, Astra, Dr. Esteve, FAES, GSK, Lacer, Leti, MSD, Novartis, Schering-Plough, Stallergenes, UCB, Uriach; Marta Ferrer Puga with: UCB; Ignacio Jáuregui Presa with: FAES, Novartis, UCB, Schering-Plough, MSD, Nycomed, Chiesi, GSK, Almirall; Javier Montoro Lacomba with: UCB, FAES, Schering-Plough, ALK-Abelló, Uriach, GSK, Stallergenes, Novartis; Joaquim Mullol i Miret with: UCB, Uriach, Schering-Plough, MSD, GSK, Boheringer-Ingelheim, Novartis, Hurtington Pharmaceuticals, FAES; Joaquín Sastre Domínguez with: GSK, Novartis, Stallergenes, UCB, MSD, ALK-Abelló, Stallergenes, FAES; Antonio Luis Valero Santiago with: MSD, Uriach, Dr. Esteve, Chiesi, GSK, FAES, UCB, Stallergenes.

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