

# Antihistamines in the treatment of chronic urticaria

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## ■ Summary

Chronic urticaria is highly prevalent in the general population, and while there are multiple treatments for the disorder, the results obtained are not completely satisfactory. The second-generation H1 antihistamines remain the symptomatic treatment option of choice. Depending on the different pharmacokinetics and H1 receptor affinity of each drug substance, different concentrations in skin can be expected, together with different efficacy in relation to the histamine-induced wheal inhibition test - though this does not necessarily have repercussions upon clinical response. The antiinflammatory properties of the H1 antihistamines could be of relevance in chronic urticaria, though it is not clear to what degree they influence the final therapeutic result. Before moving on to another therapeutic level, the advisability of antihistamine dose escalation should be considered, involving increments even above those approved in the Summary of Product Characteristics. Physical urticaria, when manifesting isolatedly, tends to respond well to H1 antihistamines, with the exception of genuine solar urticaria and delayed pressure urticaria. In some cases of chronic urticaria, the combination of H2 antihistamines may prove effective - though only with common liver metabolism (CYP3A4 isoenzyme-mediated) H1 antihistamines, due to the existence of mutual metabolic interferences. The role of leukotriene antagonists associated to antihistamines in application to chronic urticaria remains to be clearly defined.

**Key words:** Angioedema. Cysteinyl-leukotriene antagonists. Antidepressants. H1 antihistamines. H2 antihistamines. Inflammation. Histamine. Skin response to histamine. Skin. Chronic urticaria. Autoimmune chronic urticaria. Physical urticaria.

## ■ Resumen

La urticaria crónica es una patología muy prevalente en la población general, en cuyo tratamiento se emplean multitud de fármacos sin un resultado completamente satisfactorio. Los antihistamínicos H1 de 2ª generación se mantienen como el primer tratamiento sintomático de elección. Según la distinta farmacocinética y afinidad por los receptores H1 de cada compuesto, cabe esperar distinta concentración en piel y distinta eficacia en la inhibición del habón inducido por histamina, lo que no repercute necesariamente en la respuesta clínica. Las propiedades antiinflamatorias de los antihistamínicos H1 podrían tener relevancia en la urticaria crónica, aunque no se sabe en qué grado influyen en el efecto terapéutico final. Antes de pasar a otro escalón de tratamiento, se discute si deberían incrementarse las dosis de antihistamínicos, incluso por encima de las aprobadas en ficha técnica. Las urticarias físicas, cuando ocurren de forma aislada, suelen responder bien a antihistamínicos H1, con la excepción de la verdadera urticaria solar y la urticaria retardada por presión. En algunas urticarias crónicas, la asociación de antihistamínicos H2 puede ser eficaz, pero sólo con antihistamínicos H1 de metabolismo hepático común (CYP3A4), en base a interferencias metabólicas mutuas. Aún no está bien definido el papel de los antagonistas de leucotrienos asociados a los antihistamínicos en la urticaria crónica.

**Palabras clave:** Angioedema. Antagonistas de cisteinil-leucotrienos. Antidepresivos. Antihistamínicos H1. Antihistamínicos H2. Inflamación. Histamina. Respuesta cutánea a histamina. Piel. Urticaria crónica. Urticaria crónica autoinmune. Urticarias físicas.

## 1.- Introduction: Chronic urticaria and angioedema

Urticaria and angioedema are among the most common causes of consultation in dermatology, allergology and emergency care. According to a recent population-based study [1], the prevalence of chronic urticaria in Spain is about 0.6% of the general population. The H1 antihistamines remain the first line symptomatic treatment for chronic urticaria, according to the most recent European consensus reports on the subject [2-4].

Urticaria and angioedema are similar processes [5]: both alterations are characterized by a vascular skin reaction with edema and dilatation of the postcapillary venules and lymphatic vessels of the dermis. In the case of urticaria, the phenomenon takes place within the superficial dermis, and the result is wheal production (Figure 1). In contrast, angioedema develops in the deep dermis and subcutaneous cellular tissue, resulting in swelling of the overlying tissue - particularly in more lax skin regions such as the lips or eyelids (Figure 2). Urticaria and angioedema are associated to a variable degree. Isolated angioedema is less frequent and may correspond to a different pathogenesis. It typically responds little or not at all to antihistamine therapy.

Chronic urticaria (CU) is defined as the appearance of wheals on a recurrent basis, more than twice a week, and during over 6 consecutive weeks [6]. However, this definition encompasses too many different clinical conditions, and there are other characteristics inherent to what most clinicians refer to as CU [7]:

- The wheals persist for more than an hour (a fact that distinguishes the condition from simple dermographism), and less than 24-36 hours (which differentiates the disorder from urticaria-vasculitis). The lesions may be indurated and painful.



Figure 1. Urticaria – Wheals



Figure 2. Palpebral angioedema

- The natural course is highly variable, with outbreaks and remissions that can last from a few months to more than 20 years.

- Although there usually are no systemic manifestations, patients suffer important alterations in quality of life, to a point equivalent even to that seen in severe coronary disease [8,9].

- There is no underlying food or drug allergy.

On moreover considering the histopathological features (Figure 3), CU is characterized by a perivascular infiltrate around the venules, without vasculitis or immune complex deposits, at the expense of CD4+ cells with mixed Th1 / Th2 characteristics and monocytes, no B lymphocytes, and a variable presence of granulocytes (polymorphonuclear cells (PMN), eosinophils, basophils) that form a late-phase infiltrate. Diminished peripheral basophil counts may be observed, along with eosinophil activation products (MBP, ECP), and the presence of adhesion molecules (integrins and selectins) - reflecting the existence of endothelial cell activation [10].

CU may be physical (triggered by specific physical stimuli) or idiopathic [11]. At least one-third of all idiopathic presentations are of an autoimmune nature, with the possible association of thyroid autoimmunity with or without clinically manifest hypothyroidism [12]. In addition to

the presence of antithyroid antibodies (more frequent than in the general population) [13], these patients may have IgG antibodies targeted against circulating IgE or (much more often) against the  $\alpha$  subunit of the IgE high-affinity receptor (Fc $\epsilon$ R-I) [14]. Such antibodies can be detected by skin testing with autologous serum, though the results are scantily reproducible because of the great variability depending on who performs the test [15]. They also can be detected by *in vitro* demonstration of the capacity of patient serum to induce healthy basophil degranulation [16]. Likewise, immunoblotting with patient serum can demonstrate the presence of a 30-35 kD IgG-binding band corresponding to the  $\alpha$  subunit of Fc $\epsilon$ R-I. These antibodies can appear in other autoimmune processes such as lupus or dermatomyositis, though in autoimmune CU they correspond to subclass IgG1 or IgG3, capable of activating complement and generating C5a, i.e., they are functional - a fact considered to be specific of autoimmune CU [17].

## 2. Effects of antihistamines upon the skin

Histamine plays a key role in the papule-erythema reaction typical of urticaria, and the antihistamines alleviate the itching

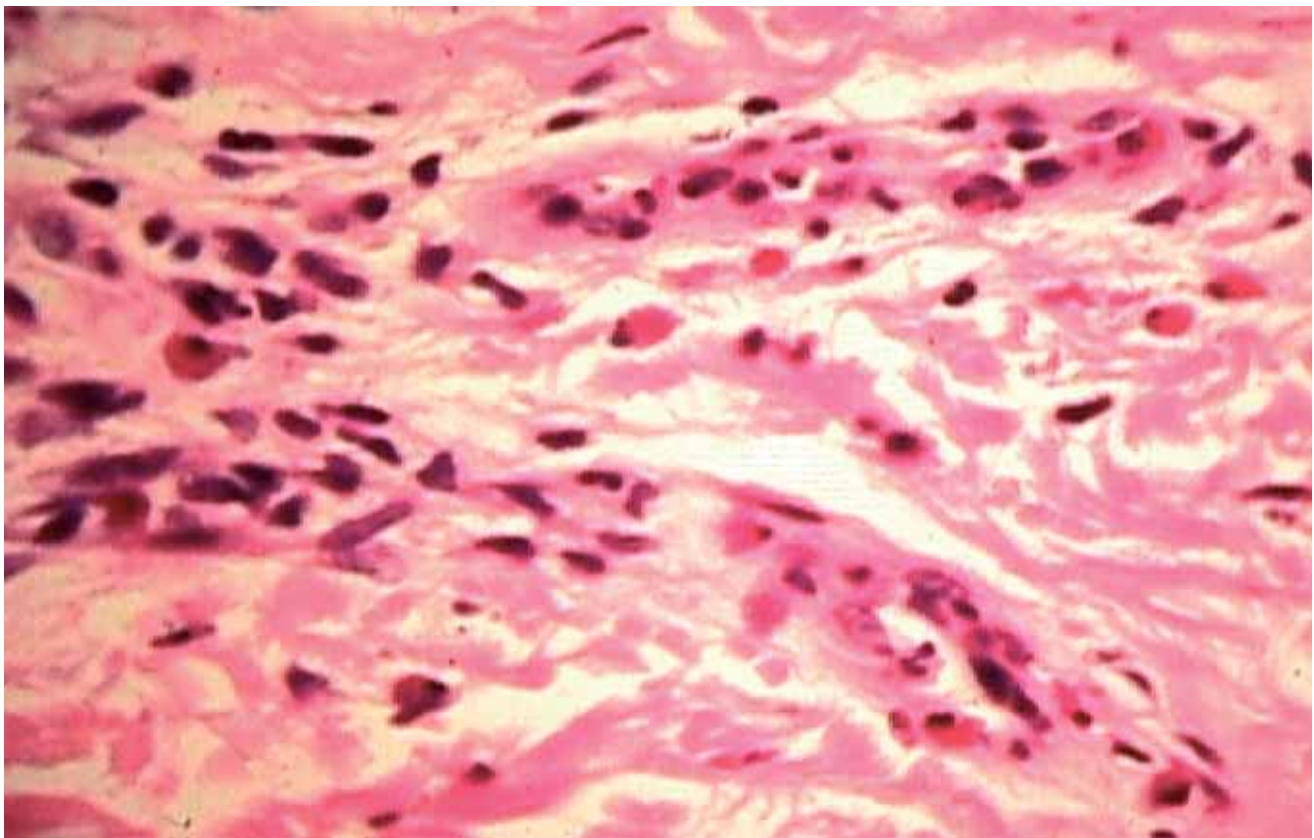


Figure 3. Urticaria – Histopathology

and reduce the number, size and duration of the urticarial lesions.

### 2.1. Mechanisms of action of the antihistamines

The efficacy of the antihistamines in application to urticaria is attributed to their H1 activity upon the afferent C nerve fibers of the skin, which reduces itching. They also act upon the axonic reflexes of the skin, which reduces erythema, and upon the endothelium of the postcapillary venules - which reduces extravasation and therefore wheal formation [18].

On the other hand, most of the antihistamines appear to possess antiinflammatory actions, including the reduction of pre- and neformed mediators, reductions in cytokine, chemokine and adhesion molecule expression - and thus reduction in inflammatory cell recruitment and inflammation [19]. These actions may be attributed mainly to two types of mechanisms:

a) Stabilization of the mast cell and basophil membranes, and inhibition of the transmembrane flux of calcium and intracellular cAMP [20]. The effect is independent of the H1 receptor, and is considered to be due to drug-membrane ionic interactions [21]. This is seen particularly *in vitro* and at experimental concentrations, and induces a decrease in preformed (histamine, tryptase) and neformed mediators (prostaglandins, leukotrienes) of the mast cells and basophils.

b) Inhibition of cytoplasmic transcription factors, such as nuclear factor kappa-B (NF- $\kappa$ B), which activates with H1 activation and migrates towards the nucleus where it interacts with nuclear DNA - stimulating the transcription of cytokines, chemokines and adhesion molecules, and the generation of nitric oxide (NO) [22] (Figure 4). The inhibition of this phenomenon is linked to interaction of the antihistamine with the H1 receptor, and is therefore to a certain extent a class effect.

Almost all the new antihistamines have been subjected to *in vitro* and *in vivo* studies in this sense (Table 1), though there are obvious differences among the different molecules. Thus, cetirizine and levocetirizine have shown anti-allergic and anti-inflammatory action even at therapeutic concentrations [19] - though in cutaneous processes such as CU, the true relevance of these anti-inflammatory properties in terms of the final therapeutic effect is not known (the importance in any case is much less than that of the glucocorticoids).

### 2.2. Antihistamines and inhibition of skin response to histamine

Since all H1 antihistamines inhibit skin reaction to histamine, the latter is considered to be a standardized biological test of antihistamine action that can be used to compare the *in vivo* effect of the different compounds [23].

In previous cross-over studies [24,25] comparing the suppression of skin papule and erythema formation induced by intradermal histamine injection following a single antihistamine dose, cetirizine was found to offer the most significant effect versus other antihistamines - the order of the inhibitory effect being as follows: cetirizine > epinastine > terfenadine > ebastine > fexofenadine > loratadine > placebo. In another study, mizolastine showed efficacy similar to that of terfenadine, with significantly less efficacy than cetirizine, and greater efficacy than loratadine [26]. Likewise, a single-

dose comparative study found levocetirizine to be the most potent of the antihistamines examined, followed by ebastine, fexofenadine and mizolastine, with similar potencies - though ebastine took four hours in eliciting an effect different from that of placebo. Loratadine was again seen to be the least potent molecule [27]. Outside the context of these studies, the antihistamine with the longest skin histamine reaction-suppressing effect (4 to 6 weeks) was found to be astemizole. This could be a result of its important distribution volume and the long elimination half-life of its principal metabolite, demethylastemizole [28]. It is interesting to comment that there is often no correlation between inhibition of the skin reaction to histamine and the clinical efficacy of the different drug compounds, when assessed in terms of symptoms scores or the impairment of patient quality of life [9].

### 2.3. Differences between plasma concentration / skin concentration

Many classical as well as second-generation antihistamines undergo first-step metabolization in the liver. As a result, their plasma levels are usually undetectable only a few hours after administration of the dose; nevertheless, the drug effect persists for much longer as a result of increased tissue concentrations of the original drug or of its active metabolites [29].

Simons compared the plasma and skin concentrations of different antihistamines, and correlated them to peripheral anti-H1 activity. He found significant differences in favor of fexofenadine 120 mg versus diphenhydramine 50 mg [30], and in favor of fexofenadine 180 mg or loratadine 10 mg versus chlorpheniramine 8 mg [18] in terms of time to action, effect,

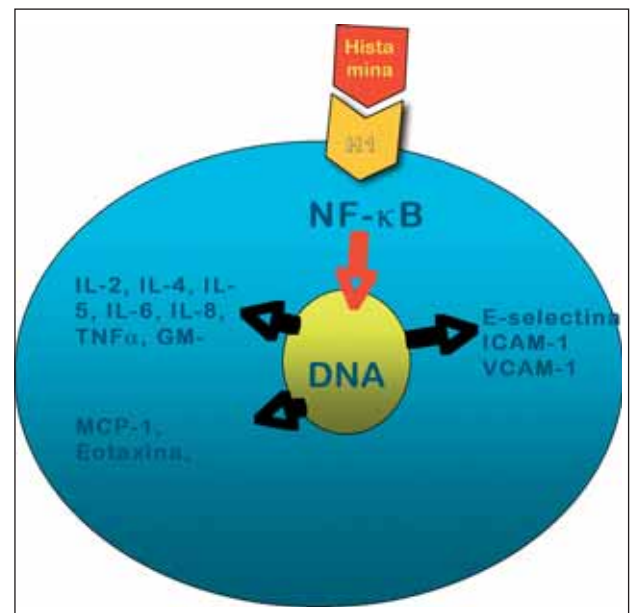


Figure 4. Anti-inflammatory effects of the antihistamines H1 receptor inactivity due to interaction with the antihistamine prevents activation of cytoplasmic transcription factors such as Nuclear Factor  $\kappa$ B (NF- $\kappa$ B), required for the expression of cytokines, chemokines and adhesion molecules.

Table 1. Inhibitory effects of antihistamines upon inflammatory cells, cytokines, chemokines and adhesion molecules

Drug	In vitro	In vivo/ex vivo
<b>Cetirizine/Levocetirizine</b>	Adhesion eosinophils <sup>67</sup> Chemotaxis eosinophils and neutrophils <sup>72</sup> Chemotaxis T lymphocytes and monocytes <sup>75</sup> Survival eosinophils <sup>76</sup> IL-8, MCP-1/ RANTES <sup>78</sup> NF-κB19	Recruit. eosinophils-skin <sup>68, 69, 70</sup> Recruit. eosinophils-bronchiole <sup>71</sup> Inhibition ICAM-1 in nasal secretion <sup>73</sup> Inhibition ICAM-1 in conjunctival secretion <sup>74</sup>
<b>Terfenadine/Fexofenadine</b> <sup>80, 81</sup>	Chemotaxis eosinophils Adherence eosinophils Generation of superoxide IL-6, IL-8, TNF-α, GM-CSF	Inhibition ICAM-1 in nasal secretion <sup>79</sup>
<b>Loratadine</b> <sup>80, 81</sup>	Chemotaxis eosinophils <sup>82</sup> IL-8, RANTES, ICAM-1s <sup>84</sup>	Recruit. eosinophils-eye <sup>83</sup> Inhibition ICAM-1 in nasal secretion <sup>85</sup> Inhibition ICAM-1 in conjunctival secretion <sup>86</sup>
<b>Desloratadine</b> <sup>87</sup>	Chemotaxis eosinophils Generation superoxide TNF-α, IL-1, IL-6, IL-8, IL-13 P-selectin, ICAM-1 Apoptosis de eosinófilos Activation NF-κB	
<b>Azelastine</b> <sup>88</sup>	Chemotaxis eosinophils Chemotaxis neutrophils Generation superoxide IL-4, IL-5 Activation NF-κB	Recruit. eosinophils-nose Inhibition ICAM-1 in nasal secretion Inhibition ICAM-1 in conjunctival secretion
<b>Mizolastine</b>	Recruit. neutrophils <sup>89</sup> 5-lipoxygenase <sup>90</sup> VEGF, TNF-α, KC <sup>91</sup>	
<b>Rupatadine</b>	PAF, TNF-α <sup>92</sup>	

ICAM-1: Intercellular adhesion molecule-1. ICAM-1s: soluble ICAM-1 (in secretions). IL-1, IL-2, etc.: Interleukin-1, Interleukin-2, etc. MCP-1: Monocyte chemotactic protein-1. RANTES: Chemokine regulated by the activation of - secreted by - and expressed in normal T cells. NF-κB: Nuclear Factor kappa-B. TNF-α: Tumor necrosis factor-alpha. GM-CSF: Granulocyte and Macrophage Colony Stimulating Factor. VEGF: Vascular Endothelial Growth Factor. KC: Keratinocyte derived chemokine. PAF: Platelet activation factor

and duration of effect. In addition, Simons demonstrated broad differences between the plasma and skin concentrations - such differences reaching a peak after 24 hours. On the other hand, this author showed that the skin concentration - not the plasma concentration - correlated to drug potency in inhibiting wheal and erythema formation in response to intradermal histamine injection. This supports the use of such second-generation antihistamines instead of first-generation drugs in application to urticaria and other skin disorders treated with antihistamines.

The skin drug concentration is also dependent upon the apparent distribution volume ( $V_d$ ), or ratio between the amount of drug in the tissues and its concentration in plasma.

$V_d$  decreases with increasing drug binding to the plasma proteins, and is directly proportional to tissue affinity for the drug compound. It would be expected that larger  $V_d$  values correspond to increased skin penetration. However, extensive tissue distribution is not considered necessary for the mechanism of action of the antihistamines, since the H1 receptor is an external receptor, and the pharmacological effect is thus achieved without cell penetration [31]. Thus, cetirizine and levocetirizine have the lowest  $V_d$  possible - a fact that exerts no influence upon their effect in terms of the inhibition of skin response, though it probably entails a lesser risk of dose-dependent toxicity and of problems derived from drug accumulation.

Lastly, there are differences among the antihistamines in terms of their H1 receptor affinity, detectable both in preclinical *in vitro* studies and in clinical trials in humans. A recent study has demonstrated significant differences between desloratadine, fexofenadine and levocetirizine in terms of *in vivo* receptor occupation after 4 and 24 hours, in direct proportion to the percentage inhibition of wheal and erythema formation (Table 2) [32].

### 3. Current tendencies in the pharmacological treatment of chronic urticaria

In chronic urticaria there are clinical trials and isolated observations with multiple treatments either as monotherapy or in combination, involving first- and second-generation antihistamines, H2 antihistamines, doxepin, other antidepressants, leukotriene antagonists, corticoids, cyclosporine and other immunosuppressors, calcineurin inhibitors, sulfasalazine, intravenous immunoglobulins, plasmapheresis or phototherapy. There are also isolated studies of experimental treatments with different immune modulators that may find applications in the future [11]: zileuton, rituximab, mycophenolate mofetil, leflunomide or the TNF- $\alpha$  inhibitors, infliximab and etanercept.

Within this potential range of treatments, the non-sedating (or second-generation) H1 antihistamines (AH-2G) are the only drugs with class 1 evidence and grade A recommendation [2-4]. They are therefore regarded as the first line symptomatic treatment option. The AH-2G offer good to moderate response in 44-91% of all types of urticaria, and in 55% of patients with CU [11].

The first-generation H1 antihistamines (AH-1G) should be reserved for those patients not controlled with AH-2G, particularly when the symptoms interfere with sleep at night [11]. All the antihistamines are more effective in alleviating itching (pruritus) than in reducing the frequency, number and size of wheals [7].

Table 2. *In vivo* occupation of H1 receptors and wheal and erythema inhibition [30]

	DL	FF	LC
Receptor occupation after 4 h (%)	71	95	90
Receptor occupation after 24 h (%)	43	12	57
Maximum wheal inhibition after 4 h (%)	34	100	100
Wheal inhibition after 24 h (%)	32	15	60
Maximum erythema inhibition after 4 h (%)	19	83	89
Erythema inhibition after 24 h (%)	41	35	74

DL: Desloratadine. FF: Fexofenadine. LC: Levocetirizine

Some authors postulate that in young adults without associated pathology, the antihistamine dosage should be raised to above the levels recommended by the manufacturer, before deciding to change or add other alternative treatments [5] - a suggestion that has class 3 evidence and grade C recommendation [3]. A recent study using cetirizine in 22 patients with severe CU contradicts this suggestion - no improvement being recorded in the second week of treatment after increasing the dose three-fold [33].

### 4. First-generation antihistamines in chronic urticaria

The antihistamines marketed before 1981 (AH-1G) share sedative and atropinic effects that probably influence low adherence to therapy - though they may be useful in patients with symptoms that interfere with sleep at night.

The most widely used in application to CU have been the ethanolamines (diphenhydramine [34], clemastine), hydroxyzine, dexchlorpheniramine, and the more classical piperidines such as cyproheptadine, azatadine and ketotifen. Ketotifen proved to be more effective than clemastine in a study involving 305 patients with CU - though the incidence of adverse effects was similar (20-21% of patients) [35].

### 5. Second-generation antihistamines in chronic urticaria

As has already been commented, the AH-2G are considered to be the first-line symptomatic treatment for CU, and are the only drugs with class 1 evidence and grade A recommendation [3], based on numerous randomized clinical trials versus both placebo and AH-1G (Tables 3 and 4).

It is a common tendency among clinicians to consider the different AH-2G to be comparable in terms of efficacy and safety. However, the AH-2G constitute a heterogeneous group of compounds with structural, antihistamine potency, pharmacological, metabolic, drug interaction and safety characteristics that differ from one molecule to another - though they share the same tissue receptors. Although it is logical to test different drugs in a given patient if some H1 antihistamine proves ineffective, we personally doubt the efficacy of combining different AH-2G with each other or with AH-1G, forcing them to compete for the same receptors and increasing the risk of drug interactions and adverse effects.

Table 4 presents several randomized clinical trials comparing cetirizine in CU versus both hydroxyzine [36] and loratadine [37], of similar clinical efficacy but with a safety profile superior to that of hydroxyzine. Although the clinical trials did not find cetirizine to alter psychomotor performance at a dose of 10 mg/day [38], some studies conducted under conditions of routine clinical practice suggest that it may cause greater subjective sedation than placebo or loratadine [39].

The antihistamine activity of cetirizine is based on the L-enantiomer, and the affinity of levocetirizine for the H1 receptors doubles that of the racemic mixture; as a result, it is considered to be pharmacologically equivalent to cetirizine at

Table 3. Treatment of chronic urticaria with second-generation antihistamines (I)

TREATMENTS	n	STUDY DESIGN	RESULTS	ADVERSE EFFECTS	AUTHOR
Cetirizina 10 / Hydroxyzine 25-75 / Placebo	219	Double blind, parallel, 4 wks.	Cetirizine = Hydroxyzine > Placebo	Drowsiness: Placebo 3%, Cetirizine 6% Hydroxyzine 15%	Kalivas, 1990 [36]
Cetirizine 10 / Placebo	30	Double blind, cross-over, 4 wks.	Cetirizine > Placebo		Juhlin, 1991 [41]
Cetirizine 10 / Loratadina 10 / Placebo	116	Double blind, parallel, 4 wks.	Cetirizine = Loratadine > Placebo	Drowsiness: Placebo 8%, Cetirizine 20% Loratadine 16%	Guerra, 1994 [37]
Loratadine 10 / Terfenadine 60x2 / Placebo	187	Double blind, parallel, 4 wks.	Loratadine > Terfenadine > Placebo	Loratadine = Terfenadine > Placebo	Belatch, 1990 [93]
Loratadine 10 / Hydroxyzine 25x3 / Placebo	172	Double blind, parallel, 4 wks.	Loratadine = Hydroxyzine > Placebo	Drowsiness: Placebo 3%, Loratadine 7% Hydroxyzine 49%	Monroe, 1992 [94]
Fexofenadine 60-120-180-240 / Placebo 1 daily dose	222	Double blind, parallel, 6 wks.	Fexofenadine > Placebo	Drowsiness and others: Fexofenadine = Placebo	Paul, 1998 [7]
Fexofenadine 60-120-180-240 / Placebo 2 daily doses	439	Double blind, parallel, 4 wks.	Fexofenadine > Placebo	Fexofenadine = Placebo (drowsiness not documented)	Finn, 1999 [42]
Mizolastine 10 / Placebo	56	Double blind, parallel, 4 wks.	Mizolastine > Placebo	Drowsiness: Mizolastine > Placebo	Brostoff, 1996 [44]
Mizolastine 10 / Loratadine 10 / Placebo	247	Double blind, parallel, 4 wks.	Mizolastine = Loratadine > Placebo	Drowsiness: Mizolastine > Loratadine	Dubertret, 1999 [7]

Table 4. Treatment of chronic urticaria with second-generation antihistamines (II)

TREATMENTS	n	STUDY DESIGN	RESULTS	ADVERSE EFFECTS	AUTHOR
Desloratadine 5 / Placebo	190	Double blind, parallel, 6 wks.	> Placebo		Ring, 2002 [95]
Desloratadine 5 / Placebo	226	Double blind, parallel, 6 wks.	> Placebo	= Placebo	Monroe, 2003 [45]
Desloratadine 5 / Desloratadine 5 + Montelukast 10 / Placebo	81	Double blind, parallel, 6 wks.	Desloratadine > Placebo Desloratadine + Montelukast > Desloratadine		Nettis, 2004 [59]
Ebastine 10 / Terfenadine 120 / Placebo	211	Double blind, parallel, 3 months	Ebastine > Placebo	= Placebo	Kalis, 1996 [43]
Rupatadine 10 / Placebo	283	Double blind, parallel, 4 wks.	Rupatadine > Placebo	= Placebo	Giménez-Arnau, 2007 [46]
Epimastine 20 / Placebo	79	Double blind, parallel, 2 wks.	Epimastine > Placebo	= Placebo	Alberto, 1997 [47]
Levocetirizine 5 / Placebo	294	Pooled Analysis (2 trials)	Levocetirizine > Placebo		Kapp, 2006 [40]
Levocetirizine 5 / Desloratadine 5 (CUTE Study)	816?	Double blind, parallel, 4 wks.	Underway (end December 2006)		

half the dosage. Levocetirizine has been studied in application to CU versus placebo in at least two trials [40], with very favorable results - particularly as refers to the number of days of itching per month ( $p < 0.001$ ). A study (the so-called CUTE survey) has also been made versus desloratadine in 816 patients divided into two homogeneous groups - though the results in this case remain to be published [41].

In relation to CU, many other AH-2G have been evaluated versus placebo, in periods of 4-6 weeks, including fexofenadine [42], ebastine [43], mizolastine [44], desloratadine [45], rupatadine [46] or epinastine [47]. The different AH-2G have also been compared with each other in the context of CU. In addition to the above mentioned study of levocetirizine versus desloratadine, trials have been made of ebastine versus terfenadine [43], cetirizine versus loratadine or mizolastine, mizolastine versus loratadine, emedastine versus loratadine [48], and others (Tables 3 and 4). In general, no significant differences are observed in the control of symptoms, patient quality of life, or safety profile.

## 6. Chronic urticaria and antihistamines in special situations

### 6.1. Pregnancy

The data available on the use of antihistamines during pregnancy are of an observational nature. Most antihistamines are classified as belonging to category B (risk not demonstrated in animals, with no human studies) or C (demonstrated risk in animals or lack of animal or human studies) of the United States Food and Drug Administration (FDA)[49](Table 5). Category B includes the AH-2G, cetirizine and loratadine; nevertheless, the AH-1G are considered the drugs of choice, since they offer greater cumulative experience [50]. It is advisable to avoid AH-1G in the third trimester of pregnancy, due to the risk of neonatal seizures [11].

### 6.2. Chronic urticaria in pediatrics

All antihistamines can be used in children over 12 years of age. In relation to the AH-1G, there are pediatric formulations for the following drugs: hydroxyzine and alimemazine (> 6 months), dexchlorpheniramine (> 1 year), diphenhydramine, clemastine, promethazine, cyproheptadine and ketotifen (> 2 years). In the case of the AH-2G, there are no pediatric formulations for fexofenadine, mizolastine or rupatadine. For the indication of CU, only cetirizine, loratadine and desloratadine are approved for treatments in patients up to 2 years of age, while ebastine and levocetirizine are only contemplated in the corresponding Summaries of Product Characteristics for urticaria in children over 6 years of age [51].

### 6.3. Kidney or liver failure

For most AH-2G, only 10-20% of the administered dose is eliminated through the kidneys - the exceptions being cetirizine (60%) and levocetirizine (85% renal elimination) [52]. On the other hand, most of these drugs undergo presystemic (first-step) metabolism in the liver, via cytochrome P-450 or CYP - the exceptions being cetirizine, levocetirizine, fexofenadine and desloratadine. In view of the above, in patients with liver or kidney failure, a reduction of the dose of all AH-2G is advised,

in accordance with the corresponding Summaries of Product Characteristics.

## 7. Other antihistamines and associations

### 7.1. Antidepressants with antihistamine action

Tricyclic antidepressants have been successfully used, including amitriptyline or doxepin [53], which possesses potent H1 antihistamine effect and H2 antihistamine activity - though use is greatly limited by the associated sedative and anticholinergic effects, reinforcement with alcohol, and the relative risk of arrhythmias - particularly as a consequence of drug interactions, resulting in prolongation of the QT interval of the ECG [7].

### 7.2. H2 antihistamines

The efficacy of H2 antihistamines in the treatment of CU is open to controversy. The blood vessels of the skin have H1 and H2 receptors, and activation of both types of receptor induces wheal and erythema formation - though H2 activation has very little effect upon the warmth and itching [7].

H1-H2 antihistamine associations have been widely used and studied. In this sense, greater efficacy has been observed for associations with H1 antihistamines presenting liver metabolism in common with H2 antihistamines, such as chlorpheniramine [54], hydroxyzine [55] or terfenadine [56], than associations with cetirizine [57]. It is thus believed that the combined effect is due more to H1-H2 antihistamine interactions at the level of CYP3A4 or other isoenzyme families - with a resulting mutual increase in the area under the plasma drug concentration-time curve (AUC) - than to any genuine "synergic effect". In view of the above, the routine use of H1-H2 antihistamine combinations is presently not justified.

### 7.3. Associations of antihistamines to leukotriene antagonists

Although not approved for use in CU, some clinical trials suggest that these associations may be of some interest in application to different types of urticaria. Montelukast has

Table 5. United States FDA risk categories for H1 antihistamines in pregnancy

Category	Compounds
B	Chlorpheniramine, dexchlorpheniramine Tripeleennamine Dimenhydrinate, doxylamine Azatadine, cyproheptadine, loratadine Hydroxyzine, cetirizine
C	Brompheniramine Diphenhydramine, carbinoxamine, clemastine Astemizole, terfenadine, fexofenadine, ebastine, mizolastine Topical H1 antihistamines: azelastine, levocabastine...



been used in CU in association to cetirizine, fexofenadine, loratadine and desloratadine, in different randomized trials [58], and in general has shown significant differences versus the antihistamine alone - at least as regards the symptoms count and results of quality of life questionnaires [59]. However, montelukast as monotherapy has not been found to be useful in CU [60]. The addition of zafirlukast to cetirizine has shown greater efficacy than placebo in patients with autoimmune CU [61], though not so in other trials involving patients with various forms of CU [62]. It has been suggested that leukotriene antagonists could be particularly interesting in patients with CU who present intolerance to aspirin or the additives - though the subject is open to controversy, and all recent reviews in the field conclude that the role of these drugs in CU has not yet been well defined [63,64].

## 8. Antihistamines in physical urticarias

The physical urticarias, where wheals are produced in response to different physical stimuli, can develop isolatedly or in association to other types of CU. With the exception of genuine solar urticaria and delayed pressure urticaria, the lesions generally tend to respond to antihistamines, used as first-line symptoms treatment in the same way as in other types of CU.

### 8.1. Dermographism (factitious urticaria)

This is the most frequent type of physical urticaria and CU. The physical stimulus giving rise to dermographism can be quantified by scratching the back of the patient with a calibrated instrument (dermographometer) [7], used to measure treatment response in many clinical trials with first- and second-generation antihistamines either alone or in combination with H2 antihistamines. In these trials superior response is observed with antihistamine versus placebo - no significant differences being recorded among the different H1 antihistamines. Dermographism is the type of CU in which the association to H2 antihistamines has yielded the best results in clinical trials [7,11].

### 8.2. Cholinergic urticaria

Cholinergic urticaria is observed in 10% of all young adults, and tends to respond to antihistamine treatment. A clinical trial with cetirizine, involving 24 well selected patients has been published [65].

### 8.3. Acquired cold urticaria

This presentation can be associated to disorders produced by cryoglobulins or other cold-reactive proteins, though in 90% of cases the condition is idiopathic [7] and responds to antihistamine therapy. Studies have been made with the piperidine antihistamines cyproheptadine, ketotifen and desloratadine, and with the piperazines cinnarizine and cetirizine - with good results in all cases. Consequently, AH2G are recommended, due to their superior tolerance profile [11].

### 8.4. Solar urticaria

This is an infrequent disorder, characterized by the development of wheals within minutes after exposure of the skin to ultraviolet or visible light. A photostimulator can be used to identify the causal wavelength. Solar urticaria is

considered to respond poorly to antihistamines. In a cohort study of 87 patients, one-third responded well to antihistamine therapy, while in 65% of cases there was only a weak or no response [66].

### 8.5. Delayed pressure urticaria

Delayed pressure urticaria develops on areas of the skin to which pressure has been applied (soles, buttocks and waist, palms of the hands after carrying heavy bags or tools), between 30 minutes and several hours after application of the pressure. It can be observed in up to 40% of all cases of CU [7], though in some patients it represents the main problem - responding poorly to antihistamines, including high-dose cetirizine and other antihistamines [7].

## 9. Conclusions

The H1 antihistamines remain the first line symptomatic treatment for chronic urticaria (evidence 1/A), according to the most recent European diagnostic and treatment consensus reports on the subject. Depending on the different pharmacokinetics,  $V_d$  and H1 receptor affinity of each drug substance, different concentrations in skin can be expected, together with different efficacy in relation to the histamine-induced wheal inhibition test - though this does not seem to imply significant differences in the comparative clinical trials. At present, we do not know the ultimate therapeutic relevance of the antiinflammatory properties of the antihistamines in relation to processes such as chronic urticaria. A number of authors suggest that before moving on to another therapeutic level, antihistamine dose escalation should be considered, involving increments even above those approved in the Summary of Product Characteristics - though this recommendation is debatable and is supported by only weak evidence. Physical urticaria, when manifesting isolatedly and not associated to other types of chronic urticaria, tends to respond well to antihistamines, with the exception of genuine solar urticaria and delayed pressure urticaria. In some cases of chronic urticaria, the combination of H2 antihistamines may prove effective - though only with common liver metabolism (CYP3A4 isoenzyme-mediated) H1 antihistamines, due to the existence of mutual metabolic interferences. In any case, this approach is generally not recommended. Likewise, there are not enough data to recommend combination with leukotriene antagonists - the role of which in chronic urticaria remains to be established.

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