

REVIEWS

H₁-antihistamines and urticaria: how can we predict the best drug for our patient?

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Summary

Urticaria, and especially chronic spontaneous urticaria (CSU), is a difficult condition to treat. Consequently, clinicians need to use the best H₁-antihistamines currently available and the pharmaceutical industries need to keep developing H₁-antihistamines that are more effective than the ones we have today. To do this we need to be able to compare the clinical efficacy of both established and new drugs. Obviously, the ideal way to do this is to use head-to-head studies in CSU. However, such studies are extremely expensive and, in the case of novel molecules, have ethical and logistical problems. Consequently, we need to have predictive models. Although determination of K_i, an indicator of the *in vitro* potency of an H₁-antihistamine, may help in the initial selection of candidate molecules, the large differences in volume of distribution and tissue accumulation in humans, precludes this from being a good predictor of clinical efficacy in CSU. From the data reviewed in this article, especially the direct comparative data of desloratadine and levocetirizine in weal and flare studies and CSU, weal and flare response would appear to be the best indicator we have of effectiveness of H₁-antihistamines in clinical practice. However, it must be pointed out that the conclusion is, essentially, based on detailed comparisons of two drugs in studies sponsored by pharmaceutical companies. Consequently, to confirm the conclusions of this review, a multicentre study independent from the influence of pharmaceutical companies should be commissioned to compare the speed of onset and effectiveness of desloratadine, fexofenadine and levocetirizine in chronic spontaneous urticaria and against histamine-induced weal and flare responses in the same patients so that we have a clear understanding of the predictive value of our models.

Keywords desloratadine, fexofenadine, H₁-antihistamines, levocetirizine, urticaria, weal and flare

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Introduction

Non-sedating H₁-antihistamines are the mainstay of treatment for urticaria [1, 2]. Clearly, there are many excellent preparations on the market today, but how can we distinguish between them? Also, what test should the pharmaceutical industry use in the development of new H₁-antihistamines. Can knowledge of basic pharmacokinetics and pharmacodynamics predict clinical effectiveness? Also, do the effects of these drugs in weal and flare studies predict potential efficacy in urticaria?

This review will focus on primarily on chronic spontaneous urticaria (CSU) characterized by the occurrence of itchy, short-lived weals ranging from a few millimetres to several centimetres in diameter which are

accompanied by severe itching which is usually worse in the evening or night-time [3]. Histamine, which is a key contributor to the symptoms of this condition, reaches very high concentrations due to the poor diffusibility of substances in the dermis [4, 5]. Standard licensed doses of H₁-antihistamines are ineffective in completely relieving symptoms in many patients for whom increasing the dosage up to fourfold is recommended [1, 6, 7]. However, the guidelines do not offer any comparisons of individual drugs.

This review will assess the potential usefulness in predicting clinical efficacy in CSU of (1) knowledge of the basic pharmacokinetics and pharmacodynamics of an H₁-antihistamine, and (2) the effectiveness of an H₁-antihistamine in weal and flare studies. To make

the comparison, the review will focus on the three H₁-antihistamines on which most comparative studies have been made; desloratadine, fexofenadine and levocetirizine.

Basic pharmacokinetics and pharmacodynamics of H₁-antihistamines

To make a preliminary prediction of the likely efficacy of an H₁-antihistamine in humans, two pieces of information are required, its absolute potency at the histamine H₁-receptor and its concentration at the sites of these receptors *in vivo*. The absolute potency or receptor affinity (K_i) is determined *in vitro* by competitive binding studies with radioactive mepyramine using isolated cells usually containing cloned H₁-receptor. Data from such experiments yield K_i values for desloratadine, levocetirizine and fexofenadine to be 0.4, 3 and 10 nm respectively [8, 9]. As the most potent drug in this test is the one which displaces mepyramine at the lowest concentration, the relative potencies of desloratadine, levocetirizine and fexofenadine are 25, 3.3 and 1. It should be emphasized herein that these experiments are performed in test tubes and cannot be extrapolated directly into *in vivo* efficacy.

The other important piece of information that is required is the drug concentration at its site of action. Theoretically, the apparent volume of distribution (V_d) of the drugs could be used to calculate such concentrations which are ~49, 0.4 and ~5.6 L/kg for desloratadine, levocetirizine and fexofenadine respectively [10]. However, volume of distribution does not take into account other factors which influence local tissue concentrations *in vivo*, such as absorption, metabolism and plasma binding. In the study of Gillard and colleagues [9], concentrations of unbound drug in the plasma rather than V_d were used to calculate receptor occupancy, a theoretical indicator of effectiveness *in vivo* (Table 1). Receptor occupancy (RO) was calculated using the equation:

$$RO(\%) = B_{\max}(100\%) \times L/(L + K_i)$$

where B_{max} is the maximal number of binding sites (set to 100%), L the plasma concentration of unbound drug and K_i the equilibrium inhibition constant.

But are potency estimates based on plasma concentrations truly indicative of clinical effectiveness? To address this, it is necessary to understand the physiology of the weal, flare and pruritus. In urticaria, histamine is released from tissue mast cells sited in the 'extravascular compartment' of the skin, i.e. in the tissues outside the blood vessels. This is mimicked by injecting histamine intradermally. The weal response has two components. The primary event is vasodilatation, described by Lewis in 1927 [11] as reddening of the skin at the site of histamine injection. This response

Table 1. Comparison of receptor occupancy for desloratadine, fexofenadine and levocetirizine with inhibition of histamine-induced weal and flare responses 4 and 24 h after drug administration

Parameter	Desloratadine	Fexofenadine	Levocetirizine
Dose (mg)	5	120	5
K _i (nm)	0.4	10	3
4 h data			
Conc free drug (nm)	1	174	28
Receptor occupancy (%)	71	95	90
Weal inhibition (%)	34	100	100
Flare inhibition (%)	19	83	89
24 h data			
Conc free drug (nm)	0.3	1.4	4
Receptor occupancy (%)	43	12	57
Weal inhibition (%)	32	15	60
Flare inhibition (%)	41	35	74

Data from reference [9].

is mediated by stimulation of H₁-receptors on the vascular smooth muscle on the extraluminal surface of the blood vessel [12]. Histamine leaking from the tissues into the circulation then stimulates H₁-receptors on the luminal surface of post-capillary venular endothelial cells to increase vascular permeability and cause an oedematous weal [13]. Because vasodilatation is the primary and dominant event of the weal response, the effectiveness of H₁-antihistamines against the weal is primarily dependent on drug concentrations in the extravascular space in the skin and influenced to a lesser extent by those within the plasma. Stimulation of the axon-reflex flare and pruritus result from the stimulation of H₁-receptors on sensory nerves exclusively in the extravascular compartment of the skin [14–16]. Thus, the flare and itch are inhibited only by drug molecules in the extravascular compartment of the dermis and not those in the circulation. From these data it is clear that it is the concentration of an H₁-antihistamine in the tissues, rather than in the blood stream, that is the primary determinant of its effectiveness.

Evidence for this is illustrated in Fig. 1 which compares the blood levels of levocetirizine with its ability to inhibit the histamine-induced weal and flare response. It is clear that plasma concentrations of levocetirizine are maximal within 1 h and yet it is not until 2 h that inhibition of the weal and flare response approaches maximal levels. This suggests that diffusion of free drug from the plasma to the extravascular space (from compartment A1 to compartment B1 in Fig. 2) is a rate limiting process in the action of H₁-antihistamines. Fig. 1 also shows that the duration of action of levocetirizine is longer than would be predicted from knowledge of plasma concentrations. This suggests that the drug is somehow sequestered and 'trapped' in the

skin, probably by binding to immobile proteins, absorption intracellularly or dissolved in lipid (compartment B2 in Fig. 2). Interestingly, the duration of inhibition of the weal is shorter than that of the flare [9, 17–19] indicating that it is also influenced by the plasma concentration of the drug.

Evidence that H_1 -antihistamines accumulate in the skin comes from a study by Frossard and colleagues [19] who showed that at 24 h after single oral doses of 5 mg, the total skin concentration (B1 + B2) of levocetirizine was approximately double that of the total plasma concentration (40 ± 19 ng/g skin vs. 20 ± 8 ng/mL plasma). Further, H_1 -antihistamines may differ considerably in the extent of their cutaneous accumulation. Twenty 4 h after a single 5 mg oral dose, the total skin concentration of desloratadine was 124 times that of the total plasma concentration (56 ± 55 ng/g skin vs. 0.45 ± 0.16 ng/mL plasma) [19]. In another study [20], while the plasma concentrations of fexofenadine fell continually between 3 and 24 h after a single oral dose of 120 mg, those in the skin remained relatively constant at around 500 ng/g of tissue. At 24 h, the skin concentrations of fexofenadine were 41.3 ± 7.8 times greater than those in the plasma.

But how and where do H_1 -antihistamines become 'trapped' within the skin? There are three possibilities.

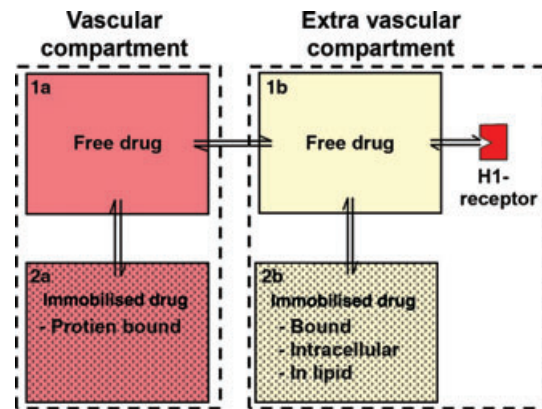


Fig. 2. A theoretical two compartment model for the effects of H_1 -antihistamines in the skin. When drugs are absorbed into the circulation, they may be present in either the free unbound form (compartment A1) or protein bound (compartment A2). The free drug in the plasma will diffuse slowly into the extravascular compartment (compartment B1) where it will be free to interact with histamine H_1 -receptors on vascular smooth muscle and nerves. However, drug entering this compartment may also become immobilized (compartment B2) by binding to proteins or extracellular matrix, becoming intracellular or being absorbed into lipid.

First, they are bound to histamine H_1 -receptors for prolonged periods. It has been published that levocetirizine, fexofenadine and loratadine dissociate from

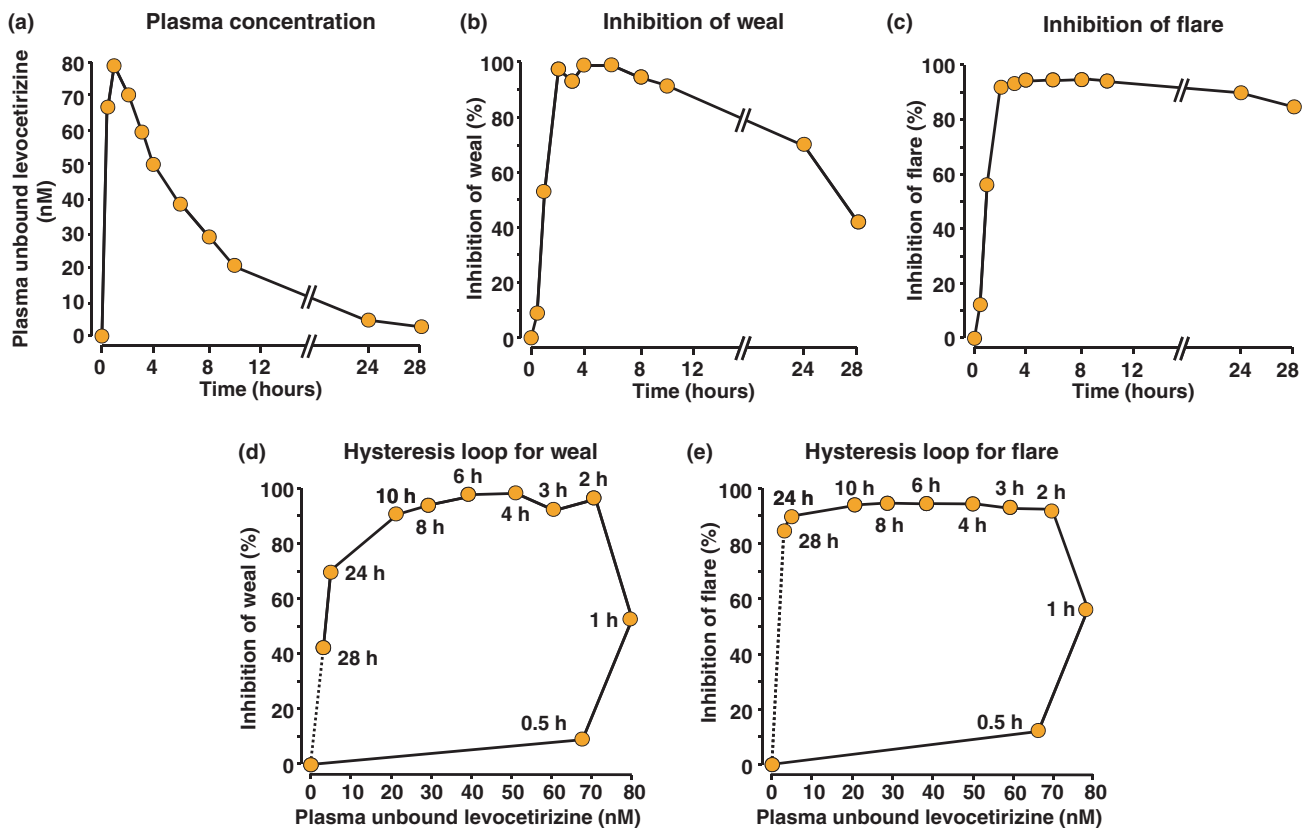


Fig. 1. Plasma concentrations, inhibitions of weal and flare responses and hysteresis plots for a single oral dose of levocetirizine. Data from references [35, 36].

histamine- H_1 receptors with half-times of 142, 62 and 5 min respectively [21]. The importance of this is not clear, particularly for drugs with short binding times. Second, they remain in the extracellular fluid and are free to interact with H_1 -receptors. Attempts were made to determine the concentrations of cetirizine in the extracellular water compartment of the skin by using microdialysis [22]. In this 3 h study, the dialysate concentrations of unbound cetirizine were only 2.4 ± 0.3 ng/mL during the 120–180 min collection period, approximately 0.3% of the plasma concentration. Third, remain present in the skin in a pharmacologically unavailable form by being bound to proteins or extracellular matrix, becoming intracellular or being absorbed into fat. The observations that with desloratadine and fexofenadine in particular [19, 20] where inhibitions of weal and flare responses were significantly lower at 24 h compared with maximal suppression at 3–4 h suggests that the third possibility has the major influence, viz. the drug present in the skin is not readily available to interact with H_1 -receptors but forms a slow release depot of drug which prolongs its pharmacodynamic activity.

In conclusion of this section, it is clear that the clinical efficacy of an H_1 -antihistamine cannot be predicted solely from knowledge of its *in vitro* potency (Ki) because *in vivo* effectiveness is influenced by many other factors, including metabolism and excretion, lipid solubility, the degree and strength of binding to proteins and structural elements, penetration into and accumulation in the tissues and, of course, the local concentration of histamine in the tissues.

Weal and flare studies

The primary *in vivo* test in humans to predict the clinical efficacy of H_1 -antihistamines is the histamine-induced weal and flare test. But is it truly predictive? Two literature-based surveys suggested that it is not. In 1997, Monroe and colleagues [23] concluded from a study of first and second generation antihistamines that although the histamine-induced weal and flare reaction can serve as a useful clinical pharmacological test to assess dose-response relations for an antihistamine, its lack of correlation with clinical responses among antihistamines indicates that this model should not be used to predict or compare clinical efficacies of antihistamines in seasonal allergic rhinitis and chronic idiopathic urticaria. Then in 2007 Devillier and Bousquet [24] published a literature search from 1980 to 2006 of 16 first and second generation antihistamines and concluded that although differences were noted between drugs in terms of their ability to inhibit histamine-induced weal and flare responses, corresponding differences in terms of clinical efficacy in allergic rhinitis

and chronic urticaria were not identified. However, good comparative data were not presented in either article and neither desloratadine nor levocetirizine featured in the lists of urticaria studies.

Let us now consider the weal and flare data for desloratadine, fexofenadine and levocetirizine. The ten weal and flare studies that have performed head-to-head comparisons of at least two of these three drugs are listed in Table 2 [9, 17–19, 25–31]. Quantifying these studies is difficult as many had different protocols. However, summarizing these data, fexofenadine and levocetirizine appear to have the greatest effect in single dose studies, both being consistently more effective than desloratadine. Similar results were found with the speed of onset, fexofenadine and levocetirizine having initial effects at 1–2 h, significantly faster than desloratadine. The maximal effect of all the drugs was at around 4 h. When weal and flare responses were provoked 24 h after dosing, levocetirizine was more effective than fexofenadine in three of four studies, suggesting levocetirizine to have a longer duration of action. Further, fexofenadine and desloratadine were of similar effectiveness in the three studies in which they were compared.

Effectiveness in clinical studies in urticaria

Three studies have performed head-to-head comparisons of levocetirizine and desloratadine in chronic idiopathic urticaria (now called chronic spontaneous urticaria [3]). Unfortunately, no studies have compared the efficacy of fexofenadine with either levocetirizine or desloratadine.

The first [32] was a multi-centre, randomized, double-blind study involving 886 patients, 438 receiving levocetirizine and 448 desloratadine. The results showed that on pruritus severity, the primary objective, levocetirizine

Table 2. Comparative effects of levocetirizine, fexofenadine and desloratadine in inhibiting the weal and flare response

Maximum effect	Speed of Onset	24 h	Reference
L5 = F180	L5 = F180	L5 > F180	[17]
L5 > D5			[25]
L5 > D5	L5 > D5	L5 > D5	[18]
L5 > D5	L5 > D5	L5 > D5	[26]
L5 = F120 > D5		L5 > F120 = D5	[9]
L5 > D5			[27]
L5 > F180 > F120 > D5	L5 > F180 > D5	L5 > F180 = D5	[28, 29]
F180 > D5	F180 > D5		[30]
L5 = F180 > D5	L5 = F180 > D5	L5 = F180 = D5	[31]
L5 > D5	L5 > D5	L5 > D5	[19]

The abbreviations used in this table are: L5, levocetirizine 5 mg; F120 and F180, fexofenadine 120 and 180 mg; and D5 desloratadine 5 mg. All drugs were given as single oral doses.

had a statistically significantly more rapid and greater effect over the first treatment week than did desloratadine (Table 3). Also, the mean scores for pruritus duration, size of weals and the composite severity score were significantly better for levocetirizine at this time. However, the number of weals score just failed to reach statistical significance. Interestingly, the significance of differences between the two drugs (Table 3) is less for all parameters over 4 weeks, suggesting that, because of its very large volume of distribution, desloratadine takes a longer period to equilibrate throughout the tissues.

The second was a 6 weeks randomized, double-blind, parallel-group pilot study of chronic spontaneous urticaria in which patients were evaluated at 2 weeks intervals [33]. In a multivariate analysis including age, gender, body mass index, renal/liver function, health problems, interactions between visits and treatments, drug changes, co-medication, and completeness of treatment, levocetirizine was independently associated with a better therapeutic response than desloratadine ($P = 0.0468$).

The third was a 4 weeks randomized, double-blind, parallel-group study to compare the effectiveness of levocetirizine and desloratadine in up to four times conventional doses in difficult-to-treat urticaria [34]. Doses were increased at weekly intervals. The cumulative numbers of the 40 patients who became symptom free on 5, 10 and 20 mg of levocetirizine were 9, 17 and 22 respectively. The corresponding values for 5, 10 and 20 mg of desloratadine were 4, 11 and 12. Furthermore, of the patients who were not symptom free on 20 mg desloratadine, switching them to levocetirizine resulted in seven becoming symptom free. In contrast, none of the patients who were not symptom free on 20 mg levocetirizine benefitted from switching to desloratadine. Analysis of VAS scores for discomfort caused by urticaria showed that levocetirizine was significantly ($P < 0.003$) more effective than desloratadine.

Table 3. Significance of difference between levocetirizine and desloratadine in the treatment of chronic spontaneous urticaria

Parameter	Significance of difference between levocetirizine and desloratadine	
	First Treatment week	Entire 4 weeks period
Pruritus severity score	$P < 0.001$	$P = 0.004$
Pruritus duration score	$P = 0.002$	$P = 0.009$
Number of weals score	$P = 0.054$	$P = 0.353$
Size of weals score	$P = 0.025$	$P = 0.085$
CSU composite score*	$P = 0.005$	$P = 0.041$

On all occasions the numerical score for levocetirizine was superior to that for desloratadine.

*Sum of the pruritus severity score and the score for the numbers of weals; CSU = chronic spontaneous urticaria. Data from reference [32].

Thus, these three clinical studies in chronic spontaneous urticaria support the hypothesis that the effectiveness of H₁-antihistamines, or at least desloratadine and levocetirizine, in the histamine-induced weal and flare test is predictive of their efficacy in the treatment of urticaria.

Conclusions

Urticaria, and especially chronic spontaneous urticaria, is a difficult condition to treat. Consequently, clinicians need to use the best H₁-antihistamines currently available and the pharmaceutical industry need to keep developing H₁-antihistamines that are more effective than the ones we have today. To do this we need to compare the clinical efficacy of both established and new drugs. Obviously, the ideal way to do this is to use head-to-head studies in CSU. However, such studies are extremely expensive and, in the case of novel molecules, have ethical and logistical problems. Consequently, we need to have predictive models. While determination of K_i, an indicator of the *in vitro* potency of an H₁-antihistamine, may help in the initial selection of candidate molecules, the large differences in volume of distribution and tissue accumulation in humans, precludes this from being a good predictor of clinical efficacy in CSU. From the data reviewed in this article, especially the direct comparative data of desloratadine and levocetirizine in weal and flare studies and CSU, weal and flare response would appear to be the best indicator we have of effectiveness of H₁-antihistamines in clinical practice. However, it must be pointed out that the conclusion is, essentially, based on detailed comparisons of two drugs in studies sponsored by pharmaceutical companies. Consequently, to confirm the conclusions of this review, a multicentre study independent from the influence of pharmaceutical companies should be commissioned to compare the speed of onset and effectiveness of desloratadine, fexofenadine and levocetirizine in chronic spontaneous urticaria and against histamine-induced weal and flare responses in the same patients so that we have a clear understanding of the predictive value of our models.

Conflict of interest

Professor Church has received honoraria for being a Speaker and/or consultant for UCB Pharma, Glaxo Smith Kline, Aventis, FAES Pharma and Schering Plough. Professor Maurer has received honoraria for being a Speaker and/or consultant for Almirall Hermal, Bayer Schering Pharma, Biofrontera, Essex Pharma, Genentech, JADO Technologies, Jerini, Merckle Recordati, Novartis, Sanofi Aventis, Schering-Plough, Leo, MSD, Merck, Shire, Symbiopharm, UCB, and Uriach.

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