

Comparing the H₁ profile of second-generation antihistamines

N. Frossard

INSERM U 425, Faculté de Pharmacie,
Université Louis Pasteur, Illkirch Cedex, France

G. M. Walsh

Department of Medicine and Therapeutics, University
of Aberdeen Medical School, Aberdeen, UK

N. Frossard
INSERM U425, BP 24
67401 Illkirch Cedex, France
Tel. +33 3 88 67 68 76
Fax: +33 3 88 67 86 38
Email: nelly.frossard@pharma.u-strasbg.fr

Introduction

For many years, oral antihistamines have been first-line medications in the treatment of allergic hypersensitivity reactions including allergic rhinitis, rhinoconjunctivitis, urticaria, and pruritus. Most patients usually expect their medication to give fast symptomatic relief from their allergies without undesirable side-effects. Although a number of mast-cell-derived mediators, including histamine, prostaglandins, and leukotrienes, are released during the anaphylactic response, the relief of symptoms given by antihistamine use indicates a major role for histamine in these reactions.

Assessment of the efficacy of the H₁-blocking drugs necessitates the use of both clinical and pharmacodynamic studies designed to compare cutaneous or nasal potency. The efficacy of an H₁-receptor antagonist may be assessed, firstly, by measuring inhibition after histamine provocation in the skin and/or the nose, a method which allows the evaluation of potential differences in drug distribution at different tissue sites. Secondly, we can assess the ability to block the response to allergen provocation in the skin, i.e., inhibition of the wheal and flare response; this approach provides information on factors such as the antigen-induced release of other mediators and also on the role that histamine plays in the symptoms of different individuals.

A number of pharmacodynamic study designs are used to compare anti-H₁ antagonist profiles. Single-dose studies provide information relating to the onset, potency, and duration of action of a drug and are the most widely used method of comparing antihistamine potency. A less common approach involves the use of

repeated dosage studies; these provide more information on absorption and metabolism of the drug and on its possible accumulation in tissues. The latter design may provide a better clinical prediction of drug efficacy.

This review is divided into three parts: the first will compare anti-H₁ profiles in skin studies; the second will discuss those studies performed in the nose; and the third will compare the effect of one antihistamine, cetirizine, in both the skin and the nose. Finally, the validity of pharmacodynamic studies as predictors of the clinical efficacy of antihistamines will be examined. It is hoped that this approach will stimulate debate about study design, and that this, in turn, may further our understanding of the validity of anti-H₁ profiles as predictors of clinical efficacy.

Pharmacodynamic studies in the skin

A reliable and reproducible method for measuring the effectiveness, onset, and duration of action of an antihistamine is to assess its ability to block the *in vitro* histamine-induced wheal and flare reaction in the skin. Histamine can be either injected intradermally or administered by skin prick test. Study design may involve either an hourly evaluation of the onset and duration of action of each drug at single or various doses (1) or a histamine concentration response at a given time point after drug intake (2, 3).

Time course of efficacy

The former design facilitates assessment of anti-H₁ activity in the 24 h after a single dosing; since the histamine concentration administered in the skin is

constant, multiple comparisons can be made of the efficacy of different drugs. Simons et al. (1) used this design in a double-blind, seven-way, crossover study that compared cetirizine (10 mg), terfenadine (60 and 120 mg), loratadine (10 mg), astemizole (10 mg), and chlorpheniramine (4 mg) with placebo for their ability to suppress histamine-induced skin wheal and flare reactions. Cetirizine was the only agent that had a significant effect, with greater than 50% inhibition of the area of wheal and flare 24 h after administration. It had a rapid onset of action and by 30 min had significantly suppressed the wheal area compared with placebo; the maximal effect was seen at 4–5 h. Loratadine was approximately half as active as cetirizine, with a maximal effect at 5 h that was still significant at 24 h.

Dose responses to histamine

In the second design, the activity and consistency of cetirizine were compared to that of ebastine 10 or 20 mg; double-blind, crossover studies were carried out to assess the inhibition of histamine dose responses on wheal and flare area 4 h after intake (2, 3). Volunteers were skin-prick-tested with increasing concentrations of histamine (0, 5, 10, 50, 100, 200, and 300 mg/ml) followed by drug administration; the test was repeated after 4 h, and the entire protocol was repeated 2 weeks later. The results were comparable between the protocols following the 2-week interval, a finding which indicates good test-test reproducibility (Fig. 1). Cetirizine almost totally inhibited the histamine-induced wheal area, ebastine 10 mg blocked slightly less than 50%, and ebastine 20 mg blocked 75% of the response (Fig. 1). Moreover, cetirizine was found to be more consistent than ebastine at each dosage; that is, it gave the least intersubject variability in suppressing cutaneous reactivity to histamine. The total inhibition of the wheal reaction at the lowest dose of histamine

was obtained in all patients, while it was demonstrated at the highest concentration in 17 out of 24 patients. In contrast, neither dosage of ebastine gave total inhibition at any histamine concentration. This finding might be a reflection of the need for ebastine to be metabolized into the active carebastine by cytochrome P450, whereas the effect of cetirizine is not dependent on biotransformation (2, 3).

Drug dosage studies

Other studies have emphasized the differences in potency between second-generation antihistamines in terms of the dosage necessary to suppress histamine-induced cutaneous reactions. In a direct comparative study, cetirizine was equipotent to loratadine, administered at four times the recommended dose, in suppressing histamine-induced wheal and flare (4); it was also superior to both loratadine (5) and ebastine (6) in reducing cutaneous blood flow, as assessed by laser Doppler flowmetry. More recently, fexofenadine has been shown to be both efficacious and safe for the treatment of ragweed-pollen allergy (7). In terms of its ability to block histamine-induced wheal and flare reactions, fexofenadine was found to be very effective, and to have a more rapid onset of action than loratadine (8).

A recent study further emphasized the potential differences between members of the second-generation class of drugs. This double-blind, crossover study compared cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine with placebo for suppression of the histamine-induced wheal and flare over a 24-h period (9). Epinastine had the most rapid onset of action, followed by cetirizine, while terfenadine induced potent inhibition which was superior to its metabolite fexofenadine. The rank order of inhibitory effect was as follows: cetirizine > epinastine > terfenadine > ebastine > fexofenadine > loratadine > placebo. Thirteen out of 14 subjects showed greater than 95% inhibition of wheal area by cetirizine; 6/14 had a similar response after treatment with terfenadine, epinastine, and ebastine; 5/14 after fexofenadine; and 2/14 after loratadine treatment (8). These findings suggest that if it is assumed that these antihistamines exhibit comparable receptor affinities, cetirizine appears to have superior dermal bioavailability.

Pharmacodynamic studies in the nose

The majority of studies which have evaluated anti-H₁ profiles have been carried out in the skin, as they are easier to perform, while, in contrast, few studies have assessed the nasal efficacy of antihistamines. These drugs are widely used for the treatment of allergic rhinitis; thus, it is necessary to measure their potency in the nose. The protocol involves the local application of

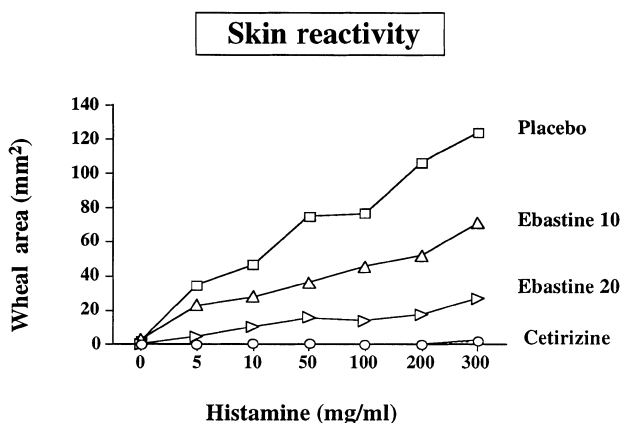


Figure 1. Effect of treatment with ebastine 10 mg and cetirizine 20 mg compared with placebo on wheal area in volunteers skin-prick-tested with increasing concentrations of histamine (0, 5, 10, 50, 100, 200, and 300 mg/ml) followed by drug administration.

histamine to the nasal mucosa. This partially mimics the response to antigen and in particular induces nasal blockage; this can be objectively measured by a technique called posterior rhinomanometry, which assesses the nasal airway resistance by both nostrils simultaneously.

Dose responses to histamine

We first carried out a double-blind, randomized, crossover, placebo-controlled study designed to assess objectively the nasal antihistamine effect of cetirizine in patients with allergic rhinitis and in control subjects (10). The study evaluated the inhibition of the histamine-induced increase in nasal airway resistance after a 3-day treatment with cetirizine 20 mg daily. Nasal challenge was performed by nebulization of incremental double doses of histamine (0; 0.04–1.28 mg/nostril) in six patients with allergic rhinitis and six control subjects taking either cetirizine or placebo. In both control subjects and patients with allergic rhinitis, cetirizine treatment resulted in a significant reduction in nasal airway resistance and perceived sensation of nasal obstruction, after dose-dependent administration of nebulized histamine (10).

Time dependence of efficacy

Posterior rhinomanometry was also used to compare the efficacy of cetirizine, loratadine, and placebo in terms of their onset and duration of action in double-blind, cross-over, placebo-controlled studies performed in patients with allergic rhinitis (11, 12). Patients who were asymptomatic at the time of the study took the single therapeutic dosage of 10 mg in each case. We assessed the maximal effects of cetirizine and loratadine at 4 h, their early effects at 1.5 h, and their late effects at 24 h. Since histamine is subjected to tachyphylaxis in the nose, the subjects were required to undergo posterior rhinomanometry on three separate occasions separated by at least 4 days: one assessed the effect 1.5 h after drug intake; another the effect at 4 h; and another at 24 h. Histamine dose responses were applied to the nasal mucosa in both nostrils, and posterior rhinomanometry was carried out at 0 (saline), 1.5, 3, 5, and 7.5 min after each nebulization. We observed a significant decrease of histamine-induced nasal airway resistance 4 h after intake; this was the maximal drug effect and was similar for both cetirizine and loratadine. The baseline was similar for all patients, and it was noted that the increase was not entirely blocked with cetirizine, as it was in the skin. At 1.5 h, histamine-induced nasal airway resistance was significantly inhibited by both cetirizine and loratadine, an effect which decreased with increasing histamine concentrations. Cetirizine was more active than loratadine, a finding which is in agreement with those obtained in the skin, and which suggests that cetirizine has a more rapid

onset of action. At 24 h, loratadine did not significantly inhibit histamine-induced nasal airway resistance compared with placebo, although there was a trend toward inhibition. In contrast, the study by Simons et al. (1) demonstrated that loratadine was still active in the skin 24 h after administration, whereas, in our study, only cetirizine had a significant effect on histamine-induced nasal airway resistance compared with placebo at the later time point. These data are summarized in Fig. 2.

The difference in the duration of the nasal action between cetirizine and loratadine might be explained by differences in their metabolism. Loratadine is rapidly metabolized to its therapeutically active form in the liver, whereas, as cetirizine does not require biotransformation, it is active immediately after absorption, being eliminated as unchanged drug. The discrepancy in the effect of loratadine at 24 h between the skin (1) and the nose (12) suggests that these types of pharmacodynamic studies should be performed at both sites, since biodistribution of the drug may differ between these organs.

Comparative study in skin and nose

In order to assess the potential effects of biodistribution in different tissues, the efficacy of cetirizine was compared in the skin and nose of patients with allergic rhinitis. Cetirizine was chosen because it is the most powerful antihistamine available in terms of suppression of histamine-induced symptoms, and it is directly active and unmetabolized. The rationale was similar to that of Wood-Baker & Holgate's study (13) in which the inhibition of bronchospasm after histamine inhalation was compared with cutaneous inhibition by a large panel of antihistamines. The results demonstrated a good correlation between the protective effect of antihistamines both in the lower airways and in the

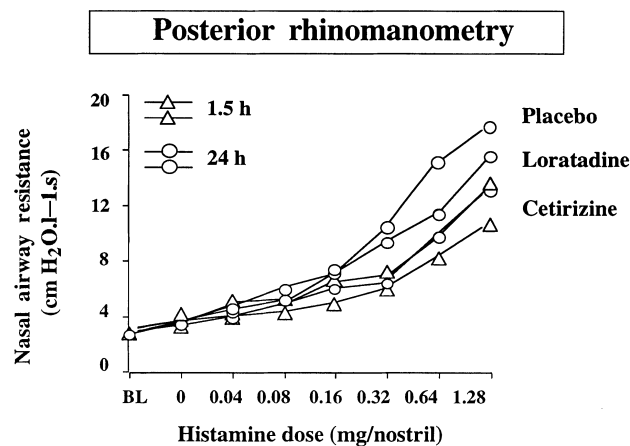


Figure 2. Effect of treatment with loratadine and cetirizine compared with placebo at 1.5 and 24 h on nasal airway resistance in volunteers skin-prick-tested with increasing concentrations of histamine (0, 5, 10, 50, 100, 200, and 300 mg/ml) followed by drug administration.

skin. We reasoned that comparison of the nasal and cutaneous activity of cetirizine would yield information on the intraindividual biodistribution of the drug.

The study was a randomized, double-blind, cross-over, placebo-controlled trial carried out over 2 months; at inclusion, subjects underwent nasal allergen provocation; 4 weeks later, they attended on 2 days separated by 1 week to undergo cutaneous or nasal histamine provocation 4 h after intake of either cetirizine or placebo. One week later, they attended on two different days separated by 1 week for nasal or skin provocation, respectively. We observed 97% inhibition by cetirizine of the histamine-induced wheal area compared to placebo and good inhibition of the nasal response, demonstrating a strongly positive effect for the drug in both organs. However, no correlation was observed between the cutaneous and nasal activities, a finding which might be explained by the fact that the inhibitory effect was almost total in the skin and only partial in the nose (Frossard et al., paper submitted). It may also be a consequence of the additional irritative effect associated with nasal provocation, something which is not seen with skin prick testing. It may be possible to improve the correlation coefficient by reducing the cetirizine dosage given in the cutaneous section of future comparative studies. Further pharmacodynamic assessment of the relative bioavailability of drugs between the two organs should improve our ability to predict the clinical efficacy of an antihistamine in both cutaneous and nasal allergic disorders.

Nasal provocation with allergen might provide additional information when assessing the potency of antihistamines and thus could be included in the pharmacoclinical group of comparative studies. In particular, informative data on the nasal efficacy of a drug could be obtained from objective measurement of airway reactivity and inflammatory parameters modified by allergen administered to the nasal mucosa at provocative or low realistic doses. This approach could, for example, include the objective measurement of nasal airway responsiveness by rhinomanometry before and after allergen exposure. The associated inflammatory events in the nasal lavage fluid could be measured in a manner analogous to recent studies that measured eosinophil cationic protein in bronchial lavage fluid before and after allergen exposure at low subclinical doses (14) and the inflammatory neuroimmune factor, nerve growth factor (15).

Conclusion

Comparison of the H_1 profile of second-generation antihistamines by pharmacodynamic studies permits a degree of objective assessment when rating the clinical efficacy of different drugs. Methodologies should

involve multiple steps and include single-dose studies which facilitate assessment of efficacy, onset and duration of action, and the consistency of interindividual efficacy. Addition of repeated dosages to this model would enhance the assessment by allowing measurement of efficacy not only at steady state but also under conditions of dynamic equilibrium, a procedure which could take account of factors such as the absorption and metabolic clearance rates of the drugs. Although Monroe et al. (16) have stated that there is not necessarily a correlation between what is observed in the skin and what is observed clinically, these types of studies nonetheless provide important information on the relative potencies of the second-generation compounds.

Discussion

Donnelly: Monroe et al. (16) report that there is not necessarily a correlation between the efficacy of an antihistamine in the skin and the clinical efficacy. The remark has to be made that if no difference emerges from a clinical study between two compounds, it does not necessarily mean that the two compounds are similar. It simply means that the study is not sensitive enough – in other words is underpowered – to detect a clinical difference, even though this may well exist.

Frossard: Indeed, the study might not be sufficiently large to demonstrate a correlation which can be shown in a pharmacodynamic study involving an agonist and its antagonist. A study of this type gives information on the efficacy of the antagonist in terms of onset and duration of action and maximal potency; it also assesses the biodistribution of a drug at different sites. It is important not to extrapolate results of efficacy from one organ site to another. Let's imagine that a good antagonist at receptor binding gives a low pharmacodynamic result in the skin; this will impair the commercialization of the drug if the test is based on that result alone. However, if the inhibitory effect in the nose was good, it would be a good drug to use in the relief of nasal allergic disorders. This subtlety was missing from Monroe et al.'s analysis. Thus, knowledge of the efficacy, onset, and duration of action of a drug at each site should be assessed before assessing the clinical efficacy.

De Vos: In terms of predictability or correlation between skin and nose for H_1 antagonists, the nose model assesses nasal blockage to histamine through posterior rhinomanometry. In real life, nasal obstructions in allergy sufferers are not due only to histamine. In seasonal allergic rhinitis, the problem is mainly sneezing. In this model, you can make a rank order of antihistaminic drugs. So my comment is that when you look at the literature like the Simons study in the skin, you have the rank order of H_1 antagonists' potency.

This order of potency is similar to that shown by Day et al. in an environmental unit (17). This indicates a correlation between skin and nose in terms of the rank of potency, which suggests it is possible to apply the predictability of this model to the clinical situation.

Frossard: Histamine nebulization induces sneezes in allergic rhinitis patients. However, there is also tachyphylaxis on sneezing to histamine. Treatment with an antihistamine, cetirizine, in our hands, entirely blocks sneezing. In addition, histamine is not the only mediator involved in the allergic response. This might be the reason for a lack of total efficacy of antihistamines in certain individuals in whom histamine has a low effect in comparison with other released mediators. However, in the case of cetirizine, there might be also an effect on other mediators released by histamine in the nasal mucosa. Secondly, by comparing the efficacy of cetirizine in the skin and nose, we were attempting to analyze the association between the cutaneous and nasal efficacies in order to assess the bioavailability of the drug. No association was detected by our study, possibly because of irritation induced by the repeated nasal provocation of increasing doses of histamine.

Timmerman: When you have an agonist and an antagonist competing for a receptor and you add a certain concentration of the agonist over a short period of time, to my mind, the efficacy would be very much dependent on the dissociation constant of the antagonist from the receptor. Has that been systematically looked at, as it might not be the absolute efficacy, but rather the receptor kinetics, which determines the difference between anti- H_1 drugs?

De Vos: There are some data available for cetirizine but I don't know if we have data for other drugs. The big surprise was that cetirizine is still effective in the histamine provocation test when you have no more than 2% in the body. Thus, I suspect cetirizine's dissociation rate to be very low.

Timmerman: In the day-to-day allergic reaction, you have continuous histamine production. There is thus a possibility that equilibrium is established because you have continuous competition between the histamine and the antagonist. If that is the case, then the test would have to be carried out over a long period to allow time for the drug to dissociate from its receptor; this suggests that a test which used a short exposure to histamine would not give a dependable result.

De Vos: In this model you give the drug first and provoke afterward, which is the usual way to study H_1

antagonists, to characterize them, to determine their onset of action and so forth. It is a different thing to determine what happens during natural exposure to allergen. The Day et al. study might provide some information on the point raised by Prof. Timmerman. It is a real model of natural exposure, an environmental chamber in which different levels of pollen are introduced. Sensitive patients are exposed in this chamber and when symptomatic are given the drug. Using this approach, the same order of potency has been observed as in the pharmacodynamic studies.

Frossard: It is necessary that the pharmacodynamic studies are performed in nonsymptomatic individuals or healthy volunteers before clinical trials, since pharmacodynamics have much to offer our understanding of the potency of a drug. If an antihistamine is only 50% active against histamine at short exposure, then either it is not rapidly absorbed or it may accumulate before full activity; this is the case for astemizole for instance. This knowledge is valuable when one wishes to perform an objective assessment after drug intake in a clinical study. Such studies are easier to conduct since they require lower numbers of volunteers; they also provide valuable data on the use of a drug: for instance, duration of action data are used to decide whether to administer a drug once or twice daily.

Rihoux: For consistency data, the dose of cetirizine might be decreased to half that normally recommended to make a valid comparison between cetirizine and ebastine. Ebastine gives a 50% inhibition, with some volunteers less and with some more; i.e., a Gaussian distribution. With cetirizine, inhibition is either complete or nearly so. Consistency could be compared at the same level of inhibition – at 50% inhibition for both drugs – decreasing the dose of cetirizine to the same effect. However, practically speaking, if the level of histamine in a tissue in humans during an allergic reaction is similar to the concentration you introduce into the skin, consistency should be very good.

Frossard: Cetirizine could be given at a lower dosage of 5 mg daily, for instance, for comparison of consistency, as for activity in the skin as compared with the nose, where the limiting step was the nearly total inhibition of skin reactivity by cetirizine at all histamine concentrations . . . in terms of pharmacodynamics also, studying efficacy and consistency at later time points might help us to understand the consistency and efficacy at maximal effect of both drugs, since ebastine seems to reach maximal activity more slowly.

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