Comparative Pharmacology of H₁ Antihistamines: Clinical Relevance

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H₁ antihistamines have similar efficacy in the treatment of allergic disorders; however, they differ in terms of their chemical structure, clinical pharmacology, and safety. This review focuses on the clinical pharmacology (pharmacokinetics and pharmacodynamics) of the newer oral H₁ antihistamines (acrivastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and mizolastine). Understanding the pharmacokinetics and pharmacodynamics of these H₁ antihistamines provides an objective basis for selection of appropriate dosages and dose intervals. Pharmacokinetic and pharmacodynamic studies provide a rationale for the modified dosage regimens that may be required in special populations, such as the very young, the elderly, those with hepatic or renal dysfunction, or those taking other medications concurrently. Many H₁ antihistamines are currently available for use. Clinical pharmacology studies help physicians to select the best H₁ antihistamines for their patients. Am J Med. 2002;113(9A):38S–46S. © 2002 by Excerpta Medica, Inc.

The H₁ antihistamines are among the most widely used of all medications. Although they have similar efficacy in the treatment of patients with allergic rhinoconjunctivitis, urticaria, and other allergic disorders, they differ with regard to chemical structure, clinical pharmacology, and potential for toxicity. The scientific foundation for using these medications with optimal effectiveness in all types of patient populations, including the very young, the elderly, those with hepatic or renal dysfunction, or those taking other medications concurrently, is documented in pharmacokinetic and pharmacodynamic studies. Pharmacokinetic studies are concerned with drug absorption, distribution, metabolism and excretion, and plasma drug concentrations over time. Pharmacodynamic studies are concerned with the relationship between drug effect and drug concentration at the site of action. Other clinical pharmacology studies that involve assessment of the antiallergic and anti-inflammatory effects of H₁ antihistamines in nasal and cutaneous challenge models will not be discussed here.

In this review, we focus on the newer orally administered H₁ antihistamines acrivastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and mizolastine, highlighting comparative studies where available. We designate all these H₁ antihistamines as second-generation, relatively non-sedating medications and avoid use of the terms “third-generation,” “next-generation,” or “new generation,” because there is, at present, no universally accepted definition of these terms.

PHARMACOKINETICS: DRUG CONCENTRATION VERSUS TIME

Traditional Pharmacokinetic Studies
Pharmacokinetic studies provide information on bioavailability, volume of distribution, protein binding, elimination half-life, clearance, and drug–drug interactions. The comparative pharmacokinetics of second-generation H₁ antihistamines in healthy young adults are shown in Table 1.

Bioavailability. The systemic bioavailability of an H₁ antihistamine is the rate at which and extent to which it reaches the blood, that is, the fraction of the dose absorbed. After oral administration, H₁ antihistamines are generally well absorbed, with peak plasma concentrations being reached within 1 to 3 hours after administration to fasting individuals (Table 1). Bioavailability is influenced by several different types of drug transporters, in-
<table>
<thead>
<tr>
<th>Drug (Metabolite)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (hr)</th>
<th>t&lt;sub&gt;1/2β&lt;/sub&gt; (hr)</th>
<th>Vd (L/kg)</th>
<th>Protein Binding (%)</th>
<th>Ae&lt;sub&gt;24&lt;/sub&gt; in Urine/Feces (%)</th>
<th>Onset of Action (hr)</th>
<th>Duration of Action (hr)</th>
<th>Population in Which Dose Adjustment May Be Required*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrivastine (none)†</td>
<td>1.4 ± 0.4</td>
<td>1.4–3.1</td>
<td>0.64</td>
<td>50</td>
<td>59/0</td>
<td>0.5</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>Cetirizine (none)</td>
<td>1.0 ± 0.5</td>
<td>6.5–10</td>
<td>0.56</td>
<td>93</td>
<td>60/0</td>
<td>0.7</td>
<td>≥24</td>
<td>Hepatic or renal dysfunction</td>
</tr>
<tr>
<td>Desloratadine (6 metabolites)</td>
<td>3</td>
<td>27</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>≥24</td>
<td>None</td>
</tr>
<tr>
<td>Ebastine&lt;sup&gt;‡&lt;/sup&gt; (carebastine)</td>
<td>(2.6–5.7)</td>
<td>(10.3–19.3)</td>
<td>(90–123)</td>
<td>&gt;95</td>
<td>(75–95)/0</td>
<td>1–3</td>
<td>≥24</td>
<td>Hepatic or renal dysfunction, Hepatic dysfunction</td>
</tr>
<tr>
<td>Fexofenadine (none)</td>
<td>1–3</td>
<td>14.4</td>
<td>5.8 ± 0.7</td>
<td>60–70</td>
<td>12/80</td>
<td>1–2</td>
<td>24</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Levocetirizine&lt;sup&gt;‡&lt;/sup&gt; (none)</td>
<td>0.8 ± 0.5</td>
<td>7 ± 1.5</td>
<td>0.33</td>
<td>96</td>
<td>86</td>
<td>0.5</td>
<td>&gt;24</td>
<td>Hepatic or renal dysfunction</td>
</tr>
<tr>
<td>Loratadine (12 metabolites, including desloratadine)</td>
<td>1.2 ± 0.3 (1.5 ± 0.7)</td>
<td>7.8 ± 4.2 (24 ± 9.8)</td>
<td>119 (73–76)</td>
<td>98</td>
<td>Trace</td>
<td>3–4</td>
<td>24</td>
<td>Hepatic dysfunction</td>
</tr>
<tr>
<td>Mizolastine&lt;sup&gt;‡&lt;/sup&gt; (none)</td>
<td>1.5</td>
<td>12.9</td>
<td>1.4</td>
<td>98</td>
<td>0.5/0</td>
<td>1</td>
<td>24</td>
<td>None</td>
</tr>
</tbody>
</table>

A<sub>e24</sub> = amount of parent compound excreted unchanged in 24 hours; AUC = area under the plasma concentration-time curve; C<sub>max</sub> = peak plasma drug concentration after single dose administration; t<sub>max</sub> = time from oral intake to peak plasma drug concentration; t<sub>1/2β</sub> = terminal elimination half-life; Vd = volume of distribution. Results are mean ± standard deviation.

* Dose adjustment potentially required in patients with moderate/severe hepatic or renal dysfunction, for example, Child’s class III hepatic disease or renal insufficiency with glomerular filtration rate <30 mL/min.

† Acrivastine has a propionic acid derivative metabolite, which has not been studied in humans.

‡ Not available in the United States at time of publication.
A Symposium: Comparative Pharmacology of H$_1$ Antihistamines/Simons

Including ATP-binding cassette transporters such as organic anion transport protein and P-glycoprotein. Fexofenadine is an interesting example of an H$_1$ antihistamine that is dependent on transport proteins for absorption and elimination.\textsuperscript{15} P-glycoprotein inducers, such as rifampicin and St. John’s wort, may have the potential to decrease fexofenadine absorption, and P-glycoprotein inhibitors, such as erythromycin and ketoconazole, have the potential to increase fexofenadine absorption. In addition to affecting fexofenadine absorption through the gut wall, P-glycoprotein also limits fexofenadine absorption into the brain and other organs. Thus, fexofenadine remains free from central nervous system toxicity and from cardiovascular toxicity even at doses 3 to 4 times those recommended by the manufacturer.\textsuperscript{16,17} The only known clinically relevant interaction between fexofenadine and other drugs is the decrease in fexofenadine absorption that occurs if aluminum/magnesium-containing antacids are administered within 15 minutes of a fexofenadine dose. The mechanism of this interaction is different from those described previously and involves fexofenadine, an organic acid, binding as such to magnesium and aluminum antacids.\textsuperscript{4}

**Volume of distribution.** Volume of distribution, a measure of H$_1$ antihistamine distribution throughout the body, does not usually represent a real body volume, such as total or extracellular body water or plasma. Rather, it is a proportionality factor that relates H$_1$ antihistamine concentration in the plasma to the total amount of H$_1$ antihistamine in the body, so the higher the degree of tissue distribution and binding, the lower the concentration in the plasma and the larger the volume of distribution. H$_1$ antihistamine volumes of distribution measured pharmacokinetically vary more than 100-fold, from 0.33 L/kg for levocetirizine to >100 L/kg for loratadine and ebastine, and many H$_1$ antihistamines appear to be extensively distributed into body tissues\textsuperscript{3,4} (Table 1).

**Protein binding.** Protein binding depends on the affinity of H$_1$ antihistamines for plasma proteins. The higher the protein binding, the lower the pharmacologically active unbound concentration of the H$_1$ antihistamine, or the amount available to exert systemic effects. H$_1$ antihistamines vary in amount of binding to plasma protein, from 50% for acrivastine to 98% for loratadine (Table 1).\textsuperscript{3,4}

**Elimination half-life.** The elimination half-life value, a measure of the time that elapses when the H$_1$-antihistamine concentration decreases to 50% of its previous value, is most accurately measured after absorption is complete, from the terminal linear portion of the concentration time curve\textsuperscript{18} (Figure 1), and is dependent on clearance and volume of distribution. H$_1$-antihistamine terminal elimination half-life (t$_{1/2,b}$) values range from 2 hours for acrivastine to 27 hours for desloratadine\textsuperscript{3,4} (Table 1).

**Clearance.** Clearance is a measure of the H$_1$-antihistamine elimination. It quantifies the fraction of the volume of body fluid (e.g., plasma) that is completely cleared of H$_1$ antihistamine within a given period of time and is therefore expressed as volume/time. The total body clearance of H$_1$ antihistamines is the sum of clearance from all organs and includes both hepatic and renal clearance.\textsuperscript{3,4}

Many of the second-generation, relatively non-sedating H$_1$ antihistamines, such as ebastine, desloratadine, loratadine, and mizolastine, are extensively metabolized in the hepatic cytochrome P450 (CYP450) system. Some are excreted largely unchanged in the urine and/or feces. For example, >50% of a dose of acrivastine and cetirizine is eliminated unchanged in the urine, >85% of levocetirizine is eliminated unchanged in the urine, and >85% of fexofenadine is eliminated unchanged in the feces after biliary excretion.\textsuperscript{2,4,7–14}

**Clinical Relevance of Pharmacokinetic Studies**

Second-generation oral H$_1$ antihistamines potentially requiring a dose reduction in patients with hepatic dysfunction include cetirizine, ebastine, levocetirizine, and loratadine (Table 1). Those potentially requiring a dose reduction in patients with renal dysfunction include cetirizine, ebastine, fexofenadine, and levocetirizine.

**Population Pharmacokinetics**

The basic information obtained on H$_1$ antihistamines in traditional pharmacokinetic studies performed in healthy young adults can be usefully compared with the population pharmacokinetic data obtained during phase 2 and 3 clinical trials of H$_1$ antihistamines\textsuperscript{19} (Figure 2). These trials involve thousands of volunteers with allergic disorders, in whom intermittent or “sparse” blood samples for hematology and chemistry tests, if obtained at precisely documented time intervals after administration of the H$_1$-antihistamine dose, can also be used for measurement of plasma antihistamine concentrations. This permits examination of possible influences of many clinical and biological covariates (for example, allergic disorder, dosage form, and patient age, sex, ethnicity, body weight, and hepatic/renal function) on pharmacokinetics. The major limitation of population pharmacokinetic studies is that patients with systemic disorders other than allergic disorders, including those with impaired hepatic or renal function and those who regularly use medications in addition to the H$_1$ antihistamine being studied, are usually excluded from phase 2 and 3 clinical trials.\textsuperscript{19}
Figure 1. Temporal relationships between the pharmacokinetics and pharmacodynamics of an H₁ antihistamine. In a prospective, randomized, double-blind study, plasma concentrations of fexofenadine were monitored along with their ability to suppress wheals and flares produced by epicutaneous histamine phosphate 1 mg/mL. After administration of fexofenadine 60 mg, plasma fexofenadine concentrations were monitored for 24 hours, and wheal and flare suppression was monitored for 28 hours. Peak wheal and flare suppression followed peak plasma fexofenadine concentrations and was maintained when the latter became negligible. These temporal relationships are typical of most H₁ antihistamines studied in various populations to date. (Adapted from *J Allergy Clin Immunol.*18)

Figure 2. Population pharmacokinetic analyses. A 2-compartment open model with 0-order absorption was used to describe the pharmacokinetics of mizolastine after oral administration. A heteroscedastic model was assumed. The 8 covariates introduced were pharmaceutical dosage form, age, sex, body weight, aspartate transaminase, alanine transaminase, serum creatinine, and renal creatinine clearance. The pharmacokinetic parameters of mizolastine in patients with allergic disorders were similar to those obtained in young healthy volunteers, and no particular high-risk group of patients was identified. (Reprinted with permission from *J Pharmacokinet Biopharm.*19)
PHARMACODYNAMICS: DRUG EFFECT VERSUS DRUG CONCENTRATION

The Allergic Rhinitis and Conjunctivitis Model

H1 antihistamines prevent and suppress the response to histamine or allergen in the nose and conjunctivae, as well as in other body organs. Patients with allergic rhinoconjunctivitis can be challenged with high-dose allergen exposure in group settings, and the onset and extent of their symptoms can be recorded.20 They can also be challenged intranasally or conjunctivally on an individual basis either with histamine or with allergen. In both these types of challenge studies, pretreatment with an H1 antihistamine prevents such symptoms as itching, congestion, rhinorrhea, tearing, and sneezing. In individual intranasal histamine challenge studies, direct evidence that H1 antihistamines downregulate the effect of histamine on the endothelial cells of the postcapillary venules and prevent vascular leakage can be obtained by measuring $\alpha_2$-macroglobulin in nasal secretions21 (Figure 3). In individual allergen challenge studies in the nose or eye, direct evidence of downregulation of the allergic response by H1 antihistamines can be obtained by measuring nasal lavage fluid or tear concentrations of biological markers, for example, histamine, leukotrienes, prostaglandins, cytokines, intercellular adhesion molecule (ICAM)–1 as expressed on epithelial cells, and other mediators and modulators of inflammation. Reduced concentrations of biological markers correlate with reduced nasal airway hyperreactivity and reduced nasal symptoms. These challenge studies provide useful information about the important role of histamine in the early- and late-phase responses in allergic rhinoconjunctivitis and about how H1 antihistamines downregulate allergen-induced inflammation in the nasal mucosa and conjunctivae.5,6

The Cutaneous Wheal and Flare Model

Information about the onset, intensity, and offset of H1-antihistamine activity is most commonly obtained by ob-

Figure 3. Effect on the nasal mucosa produced by intranasal and oral H1 antihistamines. In a double-blind, single-dose, crossover study, healthy individuals received azelastine nasal spray 0.254 mg/nasal cavity, or oral cetirizine 10 mg, or placebo. Histamine challenges (40 and 400 µg/L) were given 1 hour before, and 1, 6, 9, 12, and 24 hours after treatment. $\alpha_2$-Macroglobulin in the nasal lavage fluid was measured as a marker of increased vascular permeability and exudation of bulk plasma onto the nasal mucosa. From 1 to 12 hours after administration of azelastine, and from 1 to 24 hours after cetirizine, but not after placebo, the histamine-induced mucosal exudation of plasma was decreased, as shown by a significant decrease in the $\alpha_2$-macroglobulin marker (results obtained 1 hour after H1-antihistamine administration are shown). $^*P < 0.01; ^{†}P < 0.05$. (Reprinted with permission from Clin Exp Allergy.21)
jectively measuring the suppression of the histamine-induced wheal and flare response, or the allergen-induced wheal and flare response, to which histamine is the major contributor. \( \text{Figure 4} \) H\(_1\) antihistamines decrease the size of the wheal directly by acting on endothelial cells to decrease postcapillary venule permeability and leakage of plasma protein, and they decrease the size of the flare indirectly by blocking the histamine-induced axon reflex. Using a standardized wheal and flare bioassay, dose-response curves can be identified for an H\(_1\) antihistamine, and significant differences in onset, amount, and duration of activity among H\(_1\) antihistamines can be identified during the first 24 hours after administration.

Pharmacokinetic and pharmacodynamic studies, which have objective end points, contrast with traditional efficacy studies in allergic rhinoconjunctivitis or urticaria in which subjective symptom scores are used, and in which it is seldom possible to demonstrate clinically relevant differences between different H\(_1\) antihistamines or between different doses of the same antihistamine.
Onset of action and peak action. The pharmacodynamics of H1 antihistamines are medication and dose dependent. The peak plasma concentration (Cmax) of the H1 antihistamines in target organs, such as the skin, is achieved rapidly after oral administration (Figure 5) and correlates well with onset and amount of H1 antihistamine activity, as evidenced by significant suppression of the histamine-induced wheals and flares, which occurs within 0.5 hours (acrivastine, cetirizine) to 3 hours (loratadine) (Table 1). Peak suppression of the histamine-induced wheals and flares by H1 antihistamines generally occurs 4 to 8 hours after oral administration of a single dose, which is later than the Cmax. Maximum H1 activity usually persists for hours even after plasma concentrations have decreased to the lowest limits of analytical detection. Few H1 antihistamines have been studied directly and concomitantly in plasma and tissue. Where these studies have been performed, for example, using cetirizine (Figure 5).
ine or fexofenadine. This persistent effect is associated with high tissue/plasma concentration ratios (Figure 5). For other H₁ antihistamines, such as desloratadine, ebastine, and loratadine, the presence of active metabolites in tissue is probably important, although they have not been directly measured in tissue.

**Duration of action and residual action.** The duration of action of a single dose of an H₁ antihistamine, assessed objectively from suppression of the histamine- or allergen-induced wheals and flares in the skin, or subjectively by suppression of nasal symptoms after allergen challenge, is more prolonged than might be expected from consideration of plasma H₁ antihistamine concentrations and t₁/2β values. Although the duration of action for acrivastine is only 8 hours, for most other H₁ antihistamines, it is at least 24 hours (Figure 1), facilitating once-daily administration. For some H₁ antihistamines, the duration of action may be even longer in the elderly and in patients with hepatic or renal dysfunction, necessitating a reduced dose or dose frequency in these populations (Table 1).

The residual action of an H₁ antihistamine is defined as the pharmacologic effects that persist for days after the medication has been discontinued. This clinically useful information defines the number of H₁-antihistamine-free days that must elapse before allergen skin tests or inhalation challenge tests can be performed without the possibility of suppression by residual H₁-antihistamine activity. Most H₁ antihistamines need to be discontinued for 5 to 6 days before these tests.

**Peripheral H₁ activity does not diminish during regular administration.** Loss of effectiveness of the peripheral H₁-receptor activity of H₁ antihistamines during regular daily administration has not been found in rigorously controlled, double-blind studies of up to 12 weeks’ duration in which the suppression of skin wheals and flares has been monitored objectively, or in clinical studies of up to 6 weeks’ duration during which symptom suppression in allergic rhinitis or urticaria has been monitored subjectively. The apparent subsensitivity to some H₁ antihistamines demonstrated years ago in some studies may be the result, in part, of the weak and inconsistent effects of some of the old H₁ antihistamines being tested.

**SUMMARY**

We have reviewed the clinical pharmacology of second-generation, orally administered H₁ antihistamines. The differences in the pharmacokinetics and pharmacodynamics among these medications directly influence recommendations for dose and administration interval in patients with allergic disorders, and facilitate their use in the very young, the elderly, and in other special populations. The importance of these clinical pharmacology studies should not be underestimated, because they provide the scientific rationale for administration of H₁ antihistamines with optimal benefit and minimal risk of adverse effects.

The ideal H₁ antihistamine does not yet exist, so new medications in this class continue to be introduced. Clinical pharmacology studies of emedastine, epinastine, rupatadine, tecastemizole, and other newly developed H₁ antihistamines will provide the scientific basis for their use in clinical trials, just as this type of study has done for the second-generation H₁ antihistamines currently in use worldwide.

**REFERENCES**


