THE VALUE OF A BROAD THERAPEUTIC INDEX FOR ANTIHISTAMINES*

F. Estelle R. Simons, MD

ABSTRACT

The therapeutic index of a histamine-1 (H1)-antihistamine is the benefit-to-risk ratio of the medication and defines the range of doses and plasma concentrations over which the drug is effective and safe. In allergic rhinoconjunctivitis and urticaria, although the efficacy profiles of currently available H1-antihistamines are similar, these agents differ greatly with regard to safety, and this contributes to their different therapeutic indices. Compared with their first-generation predecessors, the orally administered second-generation H1-antihistamines such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine have fewer central nervous system (CNS) adverse effects. However, differences exist among second-generation H1-antihistamines in terms of their effect on the CNS, with some agents having potential for dose-related CNS effects when the manufacturer's recommended dose is exceeded. Similarly, in terms of cardiac safety, although all currently marketed H1-antihistamines are safer than astemizole or terfenadine, some of the medications in this class may be more likely than others to cause cardiac toxicity under certain circumstances. A broad therapeutic index is important not only when considering the potential effects of concomitant administration of medications, herbal products, and foods on the H1-antihistamine bioavailability and efficacy, but also because patients may spontaneously increase their H1-antihistamine dose in order to obtain symptom relief. Fexofenadine is an example of an H1-antihistamine that has a broad therapeutic index beyond the manufacturer's recommended doses of 120 mg or 180 mg once daily. Fexofenadine has been shown to be effective at doses as low as 20 mg twice daily and to not cause sedation or cardiac toxicity at doses as high as 690 mg twice daily. (Advanced Studies in Medicine. 2002;2[24]:872-876)

Antihistamines are used as a first-line treatment for seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. The first-generation antihistamines, although effective in relieving the symptoms of rhinitis and urticaria, are associated with unwanted adverse effects such as sedation and impaired psychomotor function because of their lack of histamine-1 (H1)-receptor selectivity and, in particular, to their penetration into the central nervous system (CNS). Second-generation antihistamines were developed in the early 1980s with the aim of having greater specificity for the H1-receptor and less CNS penetration and, therefore, overcoming the adverse effects observed with older agents. Consequently, all of the currently available second-generation antihistamines exhibit broad therapeutic indices compared...
with their first-generation counterparts. However, the potential for CNS adverse effects still remain with some of these agents. Therefore, consideration of the therapeutic index when prescribing an antihistamine is more important than consideration of either efficacy or safety alone. This paper reviews the contributory factors involved in the evaluation of the therapeutic index of H1-antihistamines and focuses on the clinical relevance of a broad therapeutic index.

**Therapeutic Index of Antihistamines**

The therapeutic index of an H1-antihistamine is the benefit-to-risk ratio, also referred to as the efficacy-to-safety ratio, of the medication. This ratio defines the range of doses and plasma concentrations over which the drug is effective and safe. The lower limit is determined by the minimally effective dose, which is the lowest dose, or lowest plasma concentration, associated with a beneficial clinical effect. The upper limit is determined by safety, which is the highest dose, or highest plasma concentration, tolerated without adverse pharmacologic effects. Most of the second-generation antihistamines have a more favorable therapeutic index than their predecessors because of their greater relative safety. First-generation antihistamines are still widely used, as indicated by the results of a recent telephone survey that included approximately 5000 individuals in communities across the United States.1 The objective of the study was to obtain information on the use of all medications, including prescription drugs and over-the-counter medications, as well as vitamins and natural supplements, including herbal formulations, during the previous week. The survey showed that, of the 40 most commonly used drugs, the sedating H1-antihistamines diphenhydramine and chlorpheniramine were more commonly used than the non-sedating second-generation agents loratadine and fexofenadine, suggesting that further efforts are required to encourage patients and physicians alike to use the newer non-sedating H1-antihistamines.1 In addition, the survey indicated that in any given week, most US adults take at least 1 prescription or nonprescription medication, including herbal formulations, and many people take multiple agents, raising concerns regarding potential drug-drug interactions that may occur.

The differences among the newer antihistamines make evaluation of the therapeutic index an important consideration when prescribing these agents. The therapeutic index varies mainly according to the properties of the H1-antihistamine itself, and these differences are the focus of this review; however, it also depends on several other factors, such as the formulation (intranasal or oral), the disease (allergic rhinitis or urticaria), and the population (pediatric or geriatric) being treated.

**Activity of Antihistamines**

The activity of antihistamines has been determined using different in vitro and in vivo models. For example, measurement of H1-antihistamine concentrations in plasma and skin and correlation of those concentrations with their peripheral H1-receptor activity has been a useful tool for determining onset of action, relative potency, and duration of action as well as in developing optimal recommendations for the dose and dose frequency of individual agents. In a recent study, the extent of fexofenadine HCl (120 mg) and diphenhydramine (50 mg) distribution into the skin was examined, and the findings were related to peripheral H1-receptor antagonist activity. The investigators found that while the skin levels of fexofenadine correlated with H1-receptor activity, diphenhydramine neither penetrated the skin nor produced substantial H1-receptor activity.2 In another study, comparative analysis of the effects of the second-generation H1-antihistamines, levocetirizine, ebastine, fexofenadine, and loratadine, showed that these agents were all effective in suppressing the histamine-induced wheal and flare response with levocetirizine exhibiting the greatest antihistaminic activity.3

In addition, the efficacy profiles of H1-antihistamines have been established in numerous clinical studies. These studies have shown that, in general, the different H1-antihistamines have similar efficacy in the treatment of allergic rhinoconjunctivitis and urticaria.4,5 For example, the H1-antihistamines, fexofenadine, loratadine, desloratadine, and cetirizine, have all proven to be effective for the treatment of allergic rhinitis and urticaria.4,5 Furthermore, different doses of the same H1-antihistamines generally have similar efficacy profiles; that is, the dose-response curve is relatively flat. For example, when fexofenadine was administered to patients with chronic urticaria at doses of 20, 60, 120, and 240 mg twice daily, all doses significantly improved the mean total symptom score compared with placebo.6
Safet Profiles of Antihistamines

In contrast to their similar efficacy profiles, currently available H₁-antihistamines differ greatly with regard to safety, and this is the factor that primarily contributes to their different therapeutic indices. A clean safety profile is particularly important for those patient populations at an increased risk for adverse effects, such as patients with a small body mass, hepatic or renal dysfunction, pre-existing CNS or cardiac disorders, and in those using concomitant medications.

Effects on CNS and Cardiotoxicity

First-generation H₁-antihistamines such as diphenhydramine were associated with sedation and impairment, which is thought to have been a result of their ability to cross the blood-brain barrier and access CNS H₁-receptors; therefore, these agents have a narrow therapeutic index. In contrast, orally administered second-generation H₁-antihistamines, such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, have fewer CNS adverse effects compared with their first-generation predecessors and therefore have wider therapeutic indices. The improvements in CNS effects with newer agents have been confirmed in more than 50 randomized, double-blind, placebo-controlled studies in which objective measurements of sleep, learning, memory, and psychomotor function have been made at regular intervals. Although these drugs have improved features over first-generation antihistamines, second-generation H₁-receptor antagonists differ from each other in terms of their CNS effects, and many of them have the potential for dose-related CNS effects when the manufacturer’s recommended dose is exceeded. An example of the differences in CNS effects between the antihistamines was shown in a recent postmarketing surveillance study assessing the sedative profiles of fexofenadine, loratadine, cetirizine, and acrivastine. In this study, although all 4 H₁-antihistamines were associated with a low incidence of sedation, the incidence was lower with fexofenadine and loratadine than with cetirizine and acrivastine.

Fexofenadine is the only H₁-antihistamine for which safety has been extensively assessed over a wide range of doses (Figure). Consistent with other reports, a recent study by Hindmarch et al showed that fexofenadine HCl at a dose of 360 mg daily is demonstrably free from disruptive effects on aspects of psychomotor and cognitive function. Furthermore, both qualitative and quantitative data from positron-emission tomography studies have shown that fexofenadine does not bind to the H₁-receptor in the brain, suggesting that it does not cross the blood-brain barrier, thereby supporting the lack of sedation or impairment observed with this antihistamine in clinical studies.

Similarly, in terms of cardiac safety, although all currently marketed H₁-antihistamines are relatively safe compared to astemizole or terfenadine, some of the medications in this class, such as diphenhydramine, may be more likely than others to cause cardiac toxicity under certain circumstances, such as when the manufacturer’s recommended dose is greatly exceeded. Because of the concerns regarding the car-
diovascular safety of older agents, all newer agents are extensively studied to assess potential cardiotoxic effects. One of these agents, fexofenadine, was studied in controlled clinical trials involving more than 6000 patients. The findings showed that this medication does not cause QTc interval prolongation or cardiovascular side effects, including torsades de pointes.12

**Drug-Drug Interactions**
Absorption of H1-antihistamines from the gastrointestinal tract may be altered by concomitant administration of other agents. P-glycoprotein, a carrier protein that belongs to the superfamily of adenosine triphosphate (ATP)-binding cassette proteins, is involved in fexofenadine absorption. Inducers of this protein, such as grapefruit juice, decrease absorption, while inhibitors such as erythromycin or ketoconazole increase absorption.19 Because fexofenadine has a broad therapeutic index, such effects are unlikely to be clinically relevant.

Evidence has suggested that the coadministration of H1-antihistamines with certain agents, including medications, herbal products, and foods, results in the inhibition of metabolism and thereby accumulation of these agents. For the first-generation antihistamines that have a narrow therapeutic index, such increases in plasma concentrations are associated with an increased risk of adverse effects, such as sedation and even cardiotoxicity.20 Notably, differences exist among antihistamines because of variations in their metabolic profile, ranging from those that exhibit significant interactions with the hepatic cytochrome P450 isoenzymes (such as astemizole and terfenadine) to those that are practically devoid of interactions in the P450 system (such as cetirizine, fexofenadine, or levocetirizine).

In order to assess the clinical relevance of such drug-drug interactions, evaluation of the therapeutic index is particularly important. As described below, for those antihistamines that exhibit a broad therapeutic index, although such interactions may alter the plasma H1-antihistamine concentration, this is unlikely to translate into relevant changes in clinical outcomes.

**The Clinical Significance of a Wide Therapeutic Index**
Fexofenadine is an example of an H1-antihistamine that has an extremely broad therapeutic index beyond the recommended daily dose of 120 to 180 mg. In clinical studies, the minimally effective dose of fexofenadine is 20 mg twice daily, and even when administered at doses of 360 mg, 2 to 3 times the usual recommended total daily dose, fexofenadine does not cause CNS effects as assessed using objective testing.14 Furthermore, when doses of 690 mg twice daily, 6 times the recommended daily dose, were given in clinical studies, fexofenadine was not associated with subjective sedation, and steady-state plasma concentrations of up to 4900 ng/mL were shown to be well tolerated.13,18 Investigations have also shown that fexofenadine does not cause cardiovascular effects: single (up to 800 mg daily) or multiple (up to 690 mg twice daily for a period of 28 days) doses of fexofenadine administered to healthy individuals produced no clinically significant changes in cardiac conductance.12

A broad therapeutic index is valuable for an H1-antihistamine, not only in terms of potential effects of drug-drug interactions but also in situations where overcompliance occurs; that is, when patients increase their H1-antihistamine dose in order to obtain symptom relief. For drugs with a broad therapeutic index, even if the recommended dose is exceeded, the patient is unlikely to be at risk from adverse effects.

Evaluation of the therapeutic index is also important given the recent interest in the potential use of antihistamines in the treatment of asthma. In many of the clinical studies that have demonstrated the relief of asthma symptoms, H1-antihistamines have been given in higher doses than those used in the treatment of allergic rhinitis.21 Therefore, an antihistamine with a broad therapeutic index offers greater potential in terms of flexible dosing for the treatment of other allergic diseases, such as asthma, compared with a drug that has a narrow therapeutic index.

**Conclusion**
Analysis of the efficacy and safety of antihistamines is essential for determining the therapeutic index of these agents, and this is a more appropriate measure than considering either efficacy or safety alone. Because second-generation antihistamines have demonstrated significant efficacy in clinical studies, their therapeutic indices are determined primarily by safety considerations. Fexofenadine is an example of an antihistamine with a wide therapeutic index, offering potential flexibility of dosing without increased safety concerns. In the future, evaluating the therapeutic index for all antihistamines in various patient populations will be important so that these agents can be optimally prescribed.
REFERENCES


