**THE CONCEPT OF THE THERAPEUTIC WINDOW IN THE CHOICE OF H₁-RECEPTOR ANTAGONIST**

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**ABSTRACT**

Antihistamines have existed for more than 60 years. The first-generation antihistamines provided symptom relief from allergic rhinitis but were also associated with undesired side effects due to lack of receptor selectivity and central nervous system penetration. Since then, newer-generation antihistamines have been specifically developed to reduce the occurrence of side effects while still providing efficacy. Differences of cardiotoxicity and sedation still exist, however, among available antihistamines. The choice of available antihistamines, therefore, is best informed through evaluation of the therapeutic window of each medication—ie, the dose range over which a drug is efficacious while being free from side effects. A broad therapeutic window conveys the most ideal characteristics. The therapeutic window provides considerably more information for clinical considerations than standard individual terms, such as potency, efficacy, or safety, combining these characteristics into an easily attainable understanding of the agent. This paper describes the importance of conscientious choices of antihistamines through the use of a therapeutic window based on recent research. Understanding the therapeutic windows of these agents will enable physicians to make informed treatment decisions based on the requirements of the patient and characteristics of the antihistamine.

tion. By contrast, the upper limit is set by the highest dose tolerated without adverse pharmacologic effect. The therapeutic window will differ between intranasal (topical) and oral (systemic) drug administration. The issues discussed in this paper will focus on those pertaining to oral \( H_1 \)-antihistamine administration.

Within any given therapeutic window for \( H_1 \) antihistamines, a range of factors may influence the positioning of any dose, such as coadministration of food, concomitant drug therapy (eg, macrolide antibiotics), concurrent illness (eg, hepatic/renal disease), and pharmacologic interactions (eg, alcohol). For example, fexofenadine, which is licensed for the treatment of allergic rhinitis and urticaria, is an \( H_1 \) antihistamine with a very broad therapeutic window. It is clinically effective in a total daily dose as low as 40 mg,\(^1,2\) which is one third of the clinically recommended dose. Moreover, it is free from adverse CNS effects when assessed objectively at 3 times the standard therapeutic dose (360 mg daily),\(^3\) and it is free from subjective reporting of sedation at 690 mg twice daily, a dose almost 12 times the recommended daily dose.\(^1\) By contrast, the \( H_1 \) antihistamine loratadine has a very narrow therapeutic window, with the clinically recommended dose of 10 mg appearing to be both the minimally effective dose and the maximum tolerated dose.\(^4,5\) Whereas interactions or dose adjustments are highly unlikely to influence the efficacy or safety of fexofenadine, they are likely to have an effect with respect to loratadine.

\textbf{\( H_1 \)-Antihistamine Activity}

The standard \( H_1 \)-antihistamine doses selected for clinical evaluation are assessed both in the acute challenge situation to provide information on time to onset of action, maximum inhibitory effect, and duration of action and in naturally occurring clinical disease, which has greater intrinsic variability and is less rigorously controlled than the challenge studies. These challenge and “wild-disease” studies identify the \( H_1 \)-receptor antagonistic activity of all currently available \( H_1 \) antihistamines compared with placebo.\(^6\) This antagonistic activity, however, is least evident with loratadine,\(^7\) as one might anticipate when understanding the positioning of the clinically recommended dose within the therapeutic window. The receptor antagonistic activity of different \( H_1 \)-receptor antagonists can be assessed by their suppression of histamine-induced wheal and flare, a commonly used biologic assay for demonstrating the onset and duration of peripheral \( H_1 \)-receptor blockade.\(^8,9\) This pharmacodynamic evaluation model is easily reproduced, allows objective assessments to be made in both healthy volunteers and patients, and is useful as an addition to clinical studies.

\textbf{Wheal and Flare}

Wheal and flare studies have been widely used to indicate in vivo differences in the potential efficacy of second-generation antihistamines.\(^6-11\) Frossard et al recently compared the inhibition of histamine-induced wheal and flare by fexofenadine HCl 180 mg, loratadine 10 mg, and desloratadine 5 mg in a single-dose, randomized, parallel-group, double-blind, placebo-controlled study of healthy individuals.\(^11\) This study found that total inhibition of wheal, as defined by the time required to achieve 95% inhibition of wheal area, occurred between 3 and 3.5 hours following administration of fexofenadine. In contrast, total inhibition of wheal was not observed following treatment with either loratadine or desloratadine at the standard doses. These results are further corroborated in the study by Kaliner et al.\(^12\) In this randomized, double-blind, single-dose, placebo-controlled, cross-over study, it was observed that fexofenadine HCl 180 mg was significantly more effective than loratadine 10 mg (\( P < .001 \)) or placebo (\( P < .05 \)) at suppressing the flare response. Fexofenadine wheal suppression was also significant relative to that of loratadine (\( P < .05 \)) or placebo (\( P < .05 \)). In a similar study, Purohit et al compared the inhibition of histamine-induced wheal and flare by single therapeutic doses of fexofenadine HCl 180 mg and cetirizine 10 mg in a single-center, double-blind, randomized, 2-way crossover study.\(^13\) The findings showed that fexofenadine

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\caption{Therapeutic Window}
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\*The dose range over which a treatment is both effective and free from unwanted side effects.
and cetirizine are comparable in their time to occurrence of 95% inhibition of the wheal and flare reaction to histamine.

**Clinical Studies**

Although the histamine-induced wheal and flare reaction is a useful clinical pharmacologic test to assess dose-response relations for an antihistamine, thereby providing an indication of its efficacy, data from clinical studies are necessary to properly evaluate new agents. All H1 antihistamines have been shown in placebo-controlled studies to be clinically efficacious. Studies comparing different H1 antihistamines allow evaluation of both clinical efficacy and safety, and permit investigation of the comparability of their profiles. The efficacy and safety of once-daily fexofenadine 120 mg and 180 mg and cetirizine 10 mg in the treatment of seasonal allergic rhinitis (SAR) were compared in a multicenter, double-blind, randomized, parallel-group, placebo-controlled, 14-day trial. A total symptom score (TSS) was generated as the sum of scores for the following symptoms: sneezing, rhinorrhea, itchy nose/palate/throat, and itchy/watery/red eyes. The findings revealed no significant differences in treatment efficacy between fexofenadine at either dose or cetirizine; however, cetirizine was found to substantially induce fatigue and drowsiness, in contrast to the results obtained with fexofenadine.

In a similar study, fexofenadine 180 mg and cetirizine 10 mg demonstrated statistically and clinically equivalent efficacy throughout the dosing period, based on TSS in patients with moderate-to-severe SAR. This study also assessed drowsiness using a visual analog scale (VAS) by which scores were calculated based on a range from 0 (wide awake) to 100 (extremely sleepy). Differences in VAS change from baseline between treatments were observed; patients receiving cetirizine consistently reported less drowsiness than those receiving cetirizine.

In a multicenter, multinational, double-blind, parallel-group, randomized, placebo-controlled 2-week study, van Cauwenberge et al assessed the efficacy, safety, and impact on quality of life (QOL) of once-daily fexofenadine HCl 120 mg, loratadine 10 mg, or placebo in the treatment of SAR. Fexofenadine and loratadine were significantly superior to loratadine at improving nasal congestion and itchy/watery/red eyes (P ≤ .05). All treatment groups had significantly improved overall QOL from baseline (P < .0001); however, the improvement in the fexofenadine group was significantly greater compared with the loratadine (P ≤ .03) and placebo groups (P ≤ .005).

This difference between fexofenadine and loratadine may be explained by their antagonist profile. Receptor antagonists may be neutral antagonists or inverse agonists. Neutral antagonists inhibit the action of the relevant agonist but have no other intrinsic activity. Inverse agonists, while inhibiting the action of the agonist, also have additional activity independent of this property through receptor binding. This binding alters the agonist-independent G-protein coupling of the receptor, which contributes to the basal level of cell activation. Inverse agonists will thus have a broader profile of effect than pure neutral antagonists. Studies that we have undertaken with fexofenadine in vitro indicate that it acts as an inverse agonist in that it not only inhibits tumor necrosis factor alpha–induced interleukin (IL)-8 release from epithelial cells, but also reduces the level of IL-8 in the supernatant to below the unstimulated value. The additional activity of fexofenadine over loratadine on QOL and in relieving nasal obstruction in the study by van Cauwenberge et al could be explained by its ability to act as an inverse agonist.

**Drug-Drug Interactions**

The coadministration of other drugs or pharmacologically active agents may potentially modify the positioning of an H1 antihistamine within the therapeutic window by, for example, interfering with absorption or metabolism. Such changes may either reduce clinical efficacy or increase the risk of side effects. These possible consequences became most apparent when drug interactions led to the appreciation that astemizole and terfenadine had potentially serious cardiac effects due to their inhibitory actions on the potassium rectifier currents within the myocardium. Both astemizole and terfenadine undergo hepatic metabolism involving the cytochrome P450 isoenzymes. The coadministration of macrolide antibiotics, such as erythromycin, or antifungal agents, such as ketoconazole, which share the same P450 isozymes, led to the inhibition of their metabolism and a rise in their plasma levels. This interaction took these drugs out of their therapeutic window, with the potentially fatal, although very rare, consequence of the
ventricular arrhythmia, torsade de points. H1 antihistamines that do not undergo hepatic metabolism, such as fexofenadine and cetirizine, are thus free from these cytochrome P450 interactions.

Interest has more recently focused on the relevance of pharmacologic interactions involving the superfamilies of adenosine triphosphate-binding cassette proteins, such as P-glycoprotein (Pgp) and other carrier protein families, including the organic anion transporting peptide (OATP) family. Pgp is an important transport protein regulating clearance of molecules that penetrate the blood-brain barrier. Substrates for this carrier protein are rapidly cleared from the CNS and thus are not available to act on central receptors. Fexofenadine is an excellent Pgp substrate; this property makes it a safe H1 antihistamine regarding CNS sedative effects (see review by Prof Hindmarch for details of CNS effects of H1 antihistamines).

Pgp is also involved in eliminating drugs across the gastrointestinal mucosa. At this site, ketoconazole and macrolide antibiotics are known to inhibit Pgp, reducing the gastrointestinal elimination of H1 antihistamines that use this transport mechanism. For example, ketoconazole increases the plasma levels of desloratadine, and azithromycin increases the plasma levels of both desloratadine and fexofenadine. By contrast, the OATP family helps facilitate the gastrointestinal absorption of certain H1 antihistamines. This transport process is susceptible to inhibition by grapefruit juice. Studies in a small number of healthy volunteers have reported a decrease in the plasma levels of fexofenadine when taken with large quantities (1.2 L) of double-strength grapefruit juice. This reduction is, however, only about 30% and, due to the minimally effective dose being substantially lower than the effects of this reduction, there is no clinical consequence. Individuals would be unlikely to consume quantities of grapefruit juice large enough to effect this level of reduction. Consistent with the lack of clinical significance of this interaction, data from White et al demonstrated that fexofenadine significantly inhibits the histamine wheal and flare response within the skin when oral fexofenadine is coadministered with either grapefruit juice or orange juice.

Changes in the positioning of H1 antihistamines within a narrow therapeutic window will, however, lead to clinical consequences. The significance of the 40% increase in plasma levels of desloratadine when coadministered with ketoconazole is undetermined, as much less is known about the therapeutic window of this antihistamine. It is appreciated, however, that increasing the dose of drugs that have a therapeutic dose at the top end of their therapeutic window, such as cetirizine and loratadine, can lead to central effects, such as sedation and cognitive impairment. These effects could become an issue in situations in which patients overmedicate beyond the prescribed dose due to inadequate symptom control of either rhinitis or urticaria.

**Genetic Influences**

Variations in the population and among different racial populations, in terms of the metabolism of antihistamines, may theoretically alter the position of a certain drug within its known therapeutic window. Little is known about how this variable influences either the efficacy or the side-effect profile of the currently available H1-receptor antagonists. Any impact of metabolic alterations will, as for the other considerations, be more relevant to those drugs with a narrow therapeutic window, those that are administered either at the lower or upper end of this range, and those for which small alterations can take them outside their therapeutic window. The product insert for desloratadine indicates that certain populations of patients are thought to be slow metabolizers of this agent. Approximately 7% of the general population and 20% of the black population have difficulty in converting desloratadine to its active metabolite, 3-hydroxydesloratadine, and may be more susceptible to dose-related adverse events. Additional investigation of...
this issue is warranted to understand differences in individual susceptibility within the population and to better inform physicians regarding choice of antihistamine.

CONCLUSION

The appreciation of the therapeutic window for any antihistamine and the positioning of the medication within this window allow an easy evaluation of the likely impact of any dose changes or interactions that will either decrease or increase the bioavailability of that medication. Ideally, an antihistamine should be positioned centrally within a broad therapeutic window. Under such circumstances, those influences that alter bioavailability are unlikely to have any clinical consequence, and the drug can be prescribed without concern.

REFERENCES