

The concept of receptor occupancy to predict clinical efficacy: A comparison of second generation H₁ antihistamines

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ABSTRACT

Second generation H₁ antihistamines are considered first-line therapy for allergic rhinitis and chronic idiopathic urticaria, largely because of their nonsedating effects. Evaluating pharmacokinetic and pharmacodynamic parameters and clinical efficacy of a drug is important, but models to predict clinical efficacy are lacking. Receptor occupancy (RO), a predictor for human pharmacodynamics and antihistamine potency that takes into account the affinity of the drug for the receptor and its free plasma concentration, may be a more accurate way to predict a drug's clinical efficacy. This study was designed to assess the concept of RO as a surrogate for clinical efficacy, using examples of second generation oral antihistamines. A literature review was conducted using MEDLINE. Search terms included allergy, allergic rhinitis, drug efficacy, over-the-counter drugs, perennial allergic rhinitis, seasonal allergic rhinitis, second generation antihistamines, chronic idiopathic urticaria, and treatment outcomes. Abstracts and posters from recent allergy-related society meetings were also used. RO of several second generation H₁ antihistamines was derived from noncomparative and head-to-head studies. Fexofenadine and levocetirizine showed similar RO at 4 hours, both higher than that of desloratadine. Levocetirizine established higher RO than fexofenadine or desloratadine at 12 and 24 hours. RO for these agents appeared to correlate with pharmacodynamic activity in skin wheal and flare studies and with efficacy in allergen challenge chamber studies. Parameters affecting RO included time from dosing, pH, and dosing regimen. RO did not appear to be linearly related to drug concentration. Results indicate that RO is an accurate predictor of in vivo pharmacodynamic activity and clinical efficacy.

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Key words: Allergic rhinitis, antihistamine, chronic idiopathic urticaria, desloratadine, fexofenadine, histamine H₁ antagonists, levocetirizine, receptor occupancy, treatment outcome

The H₁ antihistamines are commonly used in the treatment of allergic disorders¹ and are considered first-line therapy for mild to moderate allergic rhinitis and chronic idiopathic urticaria.^{2–4} These agents act primarily as inverse agonists at the histamine H₁ receptor, thereby reducing itching, vascular permeability,¹ and the ensuing wheal associated with allergic reactions, as well as histamine-induced secretions, such as excessive nasal congestion and mucus production.

Desired clinical characteristics of H₁ antihistamines include rapid onset of action, duration of action of at least 24 hours, reproducible and high efficacy, lack of drug interaction, and few side effects.⁵ Historically, first generation H₁ antihistamines were associated with sedative and anticholinergic side effects.¹ In addition,

these agents require frequent administration to obtain the desired therapeutic effect.⁶ Second generation H₁ antihistamines were developed to minimize or alleviate such deficiencies; however, the first two of these agents (*i.e.*, astemizole and terfenadine) were associated with adverse cardiac effects under certain circumstances and were subsequently removed from the market.^{1,7} Terfenadine was replaced by fexofenadine, a safer metabolite (Fig. 1).^{1,8} At present, second generation H₁ antihistamines commonly used in the United States or Europe include cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and mizolastine.¹

The main pharmacokinetic features of the second-generation H₁ antihistamines (*i.e.*, absorption, distribution, metabolism, and excretion) have been described and compared in the literature (Table 1),^{1,5} but it is also important to describe drug potency and clinical efficacy to assess overall effectiveness. Potency is a measure of a drug's activity based on its concentration.⁹ A highly potent drug will achieve a desired effect at a lower concentration than a relatively less potent drug. Clinical effectiveness is a measure of a drug's therapeutic benefit and is dependent on a number of pharmacokinetic and pharmacodynamic parameters (*e.g.*, absorption, distribution, metabolism, and excretion).

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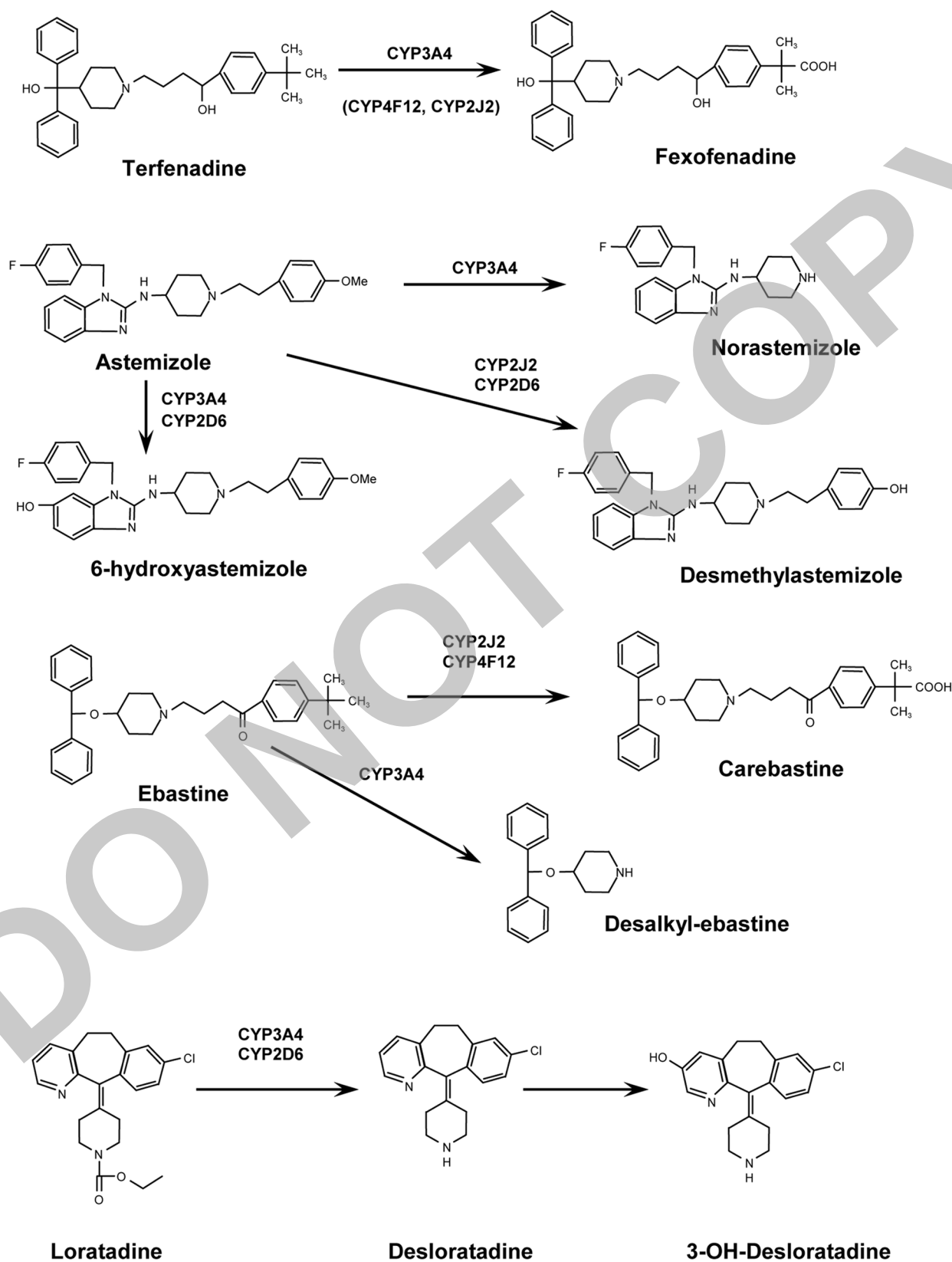


Figure 1. Chemical structures and principal metabolic pathways for some second generation H₁ antihistamines. (Reprinted with permission from Ref. 1.)

Table 1 Main pharmacokinetic and metabolic features of seven nonsedating H₁ antihistamine drugs

Features	Parameters	Cetirizine	Desloratadine	Ebastine (Carbastine)	Fexofenadine	Levocetirizine	Loratadine	Mizolastine
Absorption	T_{max} , h	1	3	3-6	2-3	0.9	1.5	1.5
Distribution	V_z/F , L/kg	0.5	49	>100	5.4-5.8	0.4	119	1.0-1.2
	Plasma protein binding, %	88-90	82-87	($\approx$ 1.3-2.0)	60-70	91	97-99	98
Metabolism	Metabolites, % dose	NA (poor metabolism)	NA (extensive metabolism)	NA (very extensive metabolism)	5	14	NA (extensive metabolism)	>65
	Enzymes involved	CYP3A4 and other multiple unidentified CYP isoforms	Enzyme(s) responsible for the formation of 3-hydroxy-desloratadine not yet identified	Mainly CYP3A4 but also CYP2J2 and 4F12	NA	CYP3A4 and other multiple unidentified CYP isoforms	Mainly CYP3A4 but also CYP1A1, 2C19, and to a lesser extent, CYP1A2, 2B6, 2C8, 2C9, 3A5	Mainly UGTs, CYP3A4
Excretion	Urine, % radioactive dose	70	41	71	11	85	40	8-15
	Feces, % radioactive dose	10	47	28	80	13	42	84-95

Source: Reprinted with permission from Ref. 1.

T_{max} = time to reach peak plasma levels of the unchanged drug; V_z/F = volume of distribution during the terminal phase/bioavailability; CYP = cytochrome P450; UGT = glucuronosyltransferase; NA = not available.

The nature of clinical effectiveness is complex and so it does not necessarily follow that a highly potent drug is also highly clinically effective.⁹

The predicted effectiveness of drugs in humans, in terms of potency and duration of action, is often based on receptor affinity measured *in vitro* and plasma half-life (Table 2).^{1,10,11} These parameters, however, do not necessarily correlate with wheal and flare inhibition. For example, desloratadine is associated with a higher affinity for human H₁-histamine receptors and a substantially longer plasma elimination half-life than fexofenadine or levocetirizine; however, the inhibition of wheal and flare produced by desloratadine has been shown to be lower and of shorter duration than that of the other two agents.¹²

Unfortunately, simply relying on affinity and plasma half-life fails to consider free drug concentration at the receptor site *in vivo*. Indeed, to be effective, an antagonist must bind to the receptor, and this event is driven by both its free concentration and affinity for the receptor.¹² Receptor occupancy (RO), a newer model for predicting clinical efficacy, has been proposed as a more accurate way to describe the clinical effectiveness of a drug. RO is a predictor of human pharmacodynamics and antihistamine potency that takes into account both the affinity of the drug for the receptor and its free plasma concentration.¹²

In humans, assessment of the potency and duration of histamine blockade at the H₁ receptor can be achieved by measuring the ability of antihistamines to inhibit the histamine-induced wheal and flare response¹²—*i.e.*, localized swelling due to plasma extravasation (wheal) and a neurovascular response involving reflex vasodilation (flare). In the current article, we show that calculation of *in vivo* RO, even if it is only an approximation, is a better and more reliable predictor of drug potency and duration of action in humans than parameters such as *in vitro* affinity and plasma half-life.

METHODS

The information for this review was compiled by searching MEDLINE for articles published through April 2008, including electronic publications available online ahead of print. Search terms used included: antihistamines, allergy, allergic rhinitis, drug efficacy, over-the-counter drugs, perennial allergic rhinitis, seasonal allergic rhinitis, second generation antihistamines, chronic idiopathic urticaria, and treatment outcomes, individually and in various combinations. Full articles were obtained and cross-referenced, and additional primary study articles were obtained. Relevant abstracts and posters from recent allergy-related society meetings were also used.

Table 2 Terms and definitions

Term	Definition
Potency	Drug activity as related to drug concentration to produce a defined effect; a highly potent agent will produce the effect at a lower dose than a less potent agent
Efficacy	Measurement of the magnitude and profile of clinical improvement of the disease after administration of an agent in a controlled setting, such as a clinical trial
Effectiveness	Measurement of the ability of a drug to typically produce a decided, claimed, or desired effect in a clinical setting
Receptor affinity	Drug concentration needed to form a significant number of drug-receptor complexes is determined by the receptor's affinity; a drug's maximal effect may be limited by the total number of receptors
Receptor occupancy	A predictor for human pharmacodynamics and antihistamine potency that takes into account both the affinity of the drug for the receptor and its free plasma concentration
K_i	Equilibrium inhibition constant is defined as the concentration of a competing ligand in a competition assay, which would occupy 50% of the receptors if no radioligand were present
Plasma half-life	The amount of time required for the drug's concentration in plasma to be reduced by half; a drug's half-life is typically considered in relation to the amount of drug in plasma, and its plasma half-life depends on how fast the drug is eliminated from the plasma
L	The free concentration of drug at the receptor site
Free plasma concentration	The amount of drug distributed in plasma that does not bind to protein; the concentration of plasma proteins and the volume of distribution influence the effect of a drug, and a higher free plasma concentration can produce a greater therapeutic effect
Elimination half-life	The amount of time it takes for the body to eliminate or break down half of a dose of a pharmacologic agent
Distribution half-life	The amount of time required to reduce the distribution of drug in various body tissues and extracellular fluids by half
Volume of distribution	The volume in which a drug would need to be distributed to produce an observed blood concentration; used to quantify the distribution of a medication throughout the body after oral or parenteral dosing. This value is usually divided by the patient's body weight and expressed in terms of liters per kilogram
Fraction unbound	The fraction of drug that is unbound by protein and remains pharmacologically active

Source: Refs. 10 and 11.

RESULTS

Calculation of *In Vivo* RO

The following formula can be used to calculate RO (RO%):

$$RO\% = B_{\max} \times \frac{[L]}{([L] + K_i)}, \quad (1)$$

where $B_{\max}$ is the maximum number of binding sites (set to 100%), $[L]$ is the free concentration of drug at the receptor site, and K_i is the equilibrium inhibition constant of the drug.^{12,13}

The value of RO will be highly dependent on the *in vitro* experimental conditions used to estimate drug

affinity (K_i).¹² Therefore, care should be taken to measure the affinity of drugs in experimental conditions that are as close as possible to those of the target tissue. Parameters that must be considered include temperature, incubation time (sufficient to reach binding equilibrium), buffer composition (salts) and pH, and biological material expressing human H_1 receptor (the affinity of a drug can be highly species dependent).¹⁴ As illustrated previously, the calculation of RO takes into account not only the affinity of drug for the receptor, but also the free drug concentrations at receptor sites.^{12,13,15}

Free plasma concentration (calculated from plasma concentration and plasma protein binding) is typically

used to estimate drug concentration at the receptor site, because only unbound drug is capable of entering and leaving the plasma and tissue compartments (assuming the absence of an active transport mechanism, at least for the target tissues containing the H₁ receptors).¹⁵ Another approach also can be used to estimate the concentration of a drug at the receptor sites, providing that the total drug concentration in the tissue containing the receptors (e.g., skin) is known. This alternative approach is based on the relationship between the volume of distribution and the fraction unbound in plasma and tissue, which allows estimation of the fraction unbound in tissue and, consequently, the free tissue concentration.¹⁵ High skin (total) concentrations of desloratadine suggest extensive tissue distribution, but not necessarily concentration at receptor sites, whereas high free skin concentration is essential for high RO.¹⁵ Notably, data estimating the concentrations of levocetirizine and desloratadine at receptor sites using the classic calculation and the volume of distribution are in reasonable agreement; thus, plasma/free skin concentrations should be used to approximate the RO of an H₁ antihistamine.¹⁵

The current discussion has focused on the estimation of RO of H₁ antihistamines using a basic equation that describes the binding of the ligand to a receptor. The equation may be further refined to take into account the presence of histamine at the receptor level as well. Indeed, histamine and the antihistamines will compete for binding to the H₁ receptors¹²:

$$RO\% = B_{\text{Max}} \times \frac{[L]}{[L] + \{K_i \times (1 + [H]/K_h)\}}, \quad (2)$$

wherein [H] is the free concentration of histamine and K_h is the equilibrium inhibition constant of histamine. When histamine is not present ([H] = 0), this equation reverts to the original one. As seen in the equation, the influence of histamine on H₁ RO by an antihistamine is dependent on the ratios [H]/K_h. In the studies described later, the simplest equation was used, because the concentration of histamine at the receptor site is unknown. However, given that histamine affinity for the H₁ receptor is rather low,¹⁶ high local free histamine concentrations would be needed to have a significant impact on RO by the antihistamines.

Histamine concentrations at the receptor site of the different tissues in physiological or pathological conditions are not known. Information is available from the literature regarding histamine concentrations in different tissues from healthy subjects, e.g., ≈8 ng/mg tissue in nasal mucosa¹⁷ and ≈20 nM in skin (perfusates of dialysis fibers, therefore, concentrations in the extracellular compartment of skin).¹⁸ Plasma histamine levels have been shown to increase from a baseline concentration of 190–905 pg/mL in 2 minutes after a

bee sting in subjects with a severe response.¹⁹ Similarly, the level of histamine in tears of patients with allergic conjunctivitis was significantly greater (23.61 ng/mL) than in healthy subjects (2.26 ng/mL).²⁰ However, because most of the tissue histamine is likely to be contained in mast cells,²¹ the aforementioned tissue concentrations probably overestimate those available at the receptor site.

When active metabolites are involved (e.g., ebastine metabolized to carebastine, hydroxyzine to cetirizine, or loratadine to desloratadine), the calculation of RO must be adjusted to take into account both the parent compound and the active metabolite free concentrations and affinities. Although the metabolite will compete with the antihistamine (and histamine), it does not matter if H₁ receptors are occupied by the antihistamine or the metabolite because, in both cases, histamine will be prevented from binding to the receptor. The following equation can be used to quantify total RO by both the metabolite and the parent compound in the presence of histamine:

$$RO\% = B_{\text{Max}} \times \left[\frac{[L]}{[L] + \left\{ K_i \times \left(1 + \frac{[H]}{K_h} + \frac{[M]}{K_m} \right) \right\}} + \frac{[M]}{[M] + \left\{ K_m \times \left(1 + \frac{[H]}{K_h} + \frac{[L]}{K_i} \right) \right\}} \right], \quad (3)$$

wherein [M] and K_m are the free concentration and the equilibrium inhibition constant of the metabolite.

Recently, Simons *et al.*, using this approach (with [H] set to 0), reported H₁ RO of hydroxyzine (the parent compound) and cetirizine (the active metabolite) when hydroxyzine is administered to healthy elderly volunteers.²² Their results clearly showed that H₁ receptors were mainly occupied by cetirizine compared with hydroxyzine (with RO ratios of 4:6 during most of the time course).

RO in the Brain

In vivo RO by H₁ antihistamines can be directly measured using positron emission tomography (PET), a noninvasive imaging technique.^{23,24} This is commonly, although not exclusively, used to measure the binding of drugs in the brain. PET has shown that second-generation antihistamines are less effective at penetrating the blood–brain barrier and thus occupy a smaller proportion of postsynaptic H₁ receptors than first-generation antihistamines.²⁴ In contrast with calculation of *in vivo* RO mentioned previously, *in vivo* RO measured using PET does not discriminate the RO due to the parent compound from that because of an active metabolite.

Table 3 Comparison of the percentages of receptor occupancy (RO) with percentages of wheal and flare inhibition at 4 and 24 hr after administration of three second generation H₁ antihistamines

Parameter	Desloratadine, 5 mg	Fexofenadine, 120 mg	Levocetirizine, 5 mg
Half-life, hr	27	14	8
Affinity, nM	0.4	10	3
Plasma protein binding, %	85	65	91
Concentration of free drug at 4 hr, nM	1	174	28
RO at 4 hr, %	71	95	90
Maximum wheal inhibition at 4 hr, %	34	100	100
Maximum flare inhibition at 4 hr, %	19	83	89
Concentration of free drug at 24 hr, nM	0.3	1.4	4
RO at 24 hr, %	43	12	57
Maximum wheal inhibition at 24 hr, %	32	15	60
Maximum flare inhibition at 24 hr, %	41	35	74

Source: Adapted with permission from Ref. 12.

Studies of RO *In Vivo*

Several recent studies, the results of which are described later, have estimated and compared *in vivo* RO for second generation H₁ antihistamines.

Comparison of RO with Levocetirizine, Desloratadine, and Fexofenadine from Different Studies

The RO of levocetirizine, desloratadine, and fexofenadine was calculated from data obtained in different studies, both after single administration and after simulating repeated administration. As mentioned, Eq. 1 has been used for the calculation, as levocetirizine and fexofenadine have no major active metabolite, and conclusive evidence of the claimed activity of the main metabolite of desloratadine (the 3-OH derivative) has not been published.

Single Dose. At 24 hours, levocetirizine had a higher percentage of RO, as well as a higher degree of wheal and flare inhibition, than either other agent (Table 3).¹² Although desloratadine has a higher receptor affinity and longer plasma elimination half-life than levocetirizine, maximum wheal inhibition at 4 hours was 34% versus 100%, respectively; furthermore, even though levocetirizine has the shortest plasma elimination half-life of the three agents, wheal inhibition at 24 hours was 60% compared with 32% with desloratadine and 15% with fexofenadine (Table 3).¹² This is because the free plasma concentration of levocetirizine at 24 hours is still higher than its affinity for the H₁ receptors, whereas this is not the case for either desloratadine or fexofenadine. The plasma half-life reported for the H₁-antihistamines is the terminal half-life (*i.e.*, the elimination half-life), which can be long but with very low plasma levels if it is preceded by a short half-life (*e.g.*,

a distribution half-life) producing a dramatic drop in plasma levels. These calculations show that the percentage of RO more accurately represents both the kinetics and the degree of inhibition of wheal and flare than the plasma elimination half-life and receptor affinity alone.¹²

Repeated Doses

Measurement of RO after repeated dosing is also important to consider, because repeated doses affect plasma concentrations by accumulation. Depending on the half-life and accumulation ratio, RO may be differentially affected for the H₁ antihistamines. The percentage of RO of levocetirizine is consistently greater than that of desloratadine and fexofenadine not only after single administration, but also after repeated administration at steady state with daily doses of levocetirizine, 5 mg; fexofenadine, 120 mg; and desloratadine, 5 mg, respectively.²⁵ Moreover the percentage of RO of levocetirizine at steady state 24 hours after the daily dose of 5 mg (60% at pH 7.4; 78% at pH 5.8) was greater than that of fexofenadine at steady state not only 24 hours after the daily dose of 120 mg (17% at pH 7.4; 20% at pH 5.8) but also 24 hours after the daily dose of 180 mg (23% at pH 7.4; 28% at pH 5.8).²⁶

Specific Studies Comparing Potency and RO

Levocetirizine versus Desloratadine. In a prospective, randomized, double-blind, placebo-controlled, single-center, three-way crossover study in 18 patients with allergy (age range, 18.5–48.1 years; female patients, 50%; race, 100% white), levocetirizine inhibited cutaneous allergic reactions to a significantly greater degree than did desloratadine ($p < 0.001$; Fig. 2).²⁷ At any time point during the 24 hours after drug intake, pa-

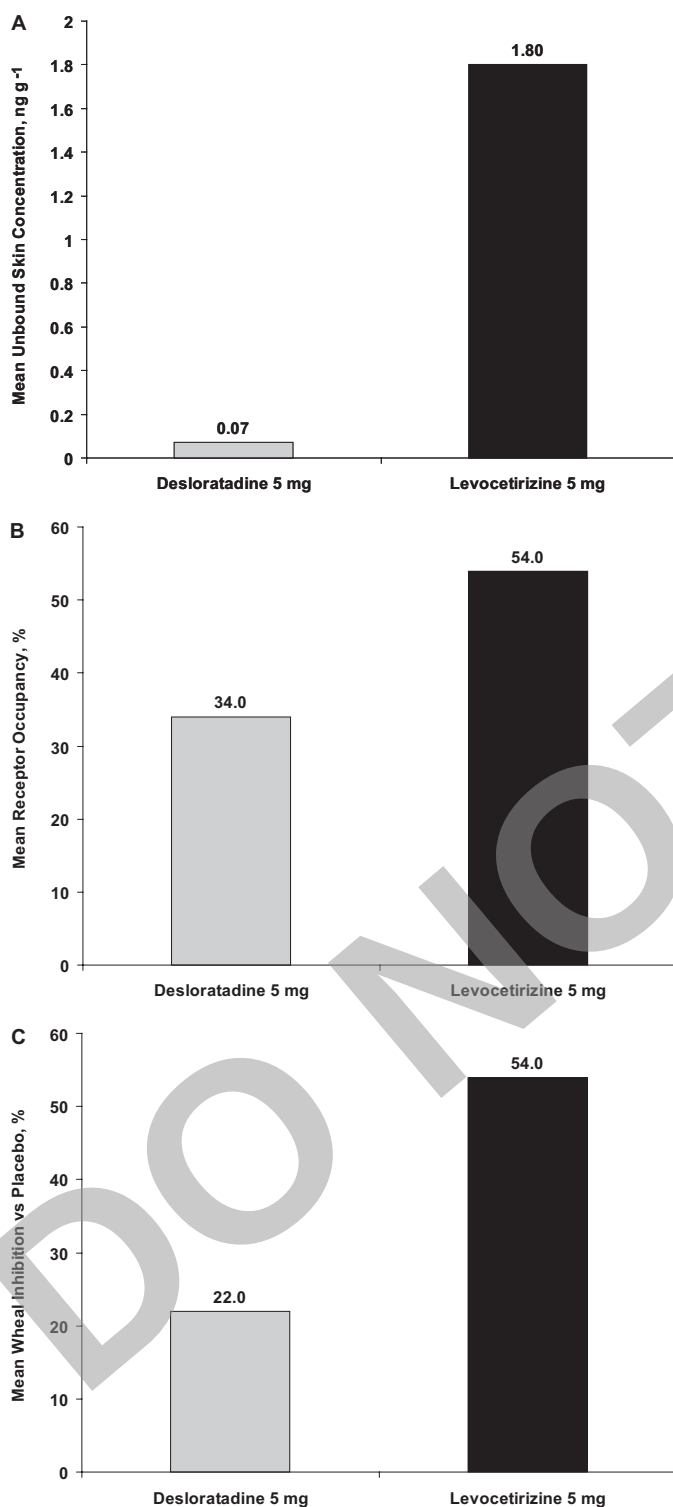


Figure 2. Shown are (A) unbound skin concentration at 24 hours after drug intake ($n = 18$), (B) receptor occupancy measured 24 hours after drug intake ($n = 18$), and (C) mean wheal inhibition at 24 hours after drug intake ($n = 18$). (Source: Ref. 27.)

tients receiving levocetirizine showed the smallest mean wheal and flare areas. Both levocetirizine and desloratadine significantly inhibited allergen-induced

wheal and flare compared with placebo ($p < 0.001$). At 1.5 hours, levocetirizine showed significant inhibition of wheal and flare compared with placebo ($p \leq 0.001$), whereas desloratadine showed a significant effect only after 4 hours. Maximum wheal inhibition occurred at 7 hours after administration of desloratadine (23%) and placebo (11%) and at 4 hours after receiving levocetirizine (72%). Maximum flare inhibition occurred at 24 hours with desloratadine (6%) and placebo (33%) and at 7 hours with levocetirizine (87%).

This study also directly measured the plasma and skin drug concentrations of levocetirizine and desloratadine, allowing calculation of RO based on these concentrations.²⁷ Mean total and unbound plasma concentration 12 and 24 hours after intake was higher with levocetirizine than desloratadine, as was mean unbound skin concentration 24 hours after intake. At 24 hours, RO based on unbound skin concentration was higher with levocetirizine (54%) than with desloratadine (34%; Table 4).^{27,28} This study confirmed the close relationship between RO and *in vivo* drug activity.

Fexofenadine versus Desloratadine. In a two-center randomized, placebo-controlled, double-blind, double-dummy, complete crossover study in 45 assessable patients (mean age, 30.9 years; female patients, 64.4%; race, 68.9% white), fexofenadine (180 mg) was shown to be significantly more effective than desloratadine, 5 mg, in inhibiting histamine-induced wheal and flare ($p < 0.0001$), suggesting that fexofenadine has increased *in vivo* H₁ receptor antagonist potency compared with desloratadine.²⁹

Fexofenadine produced significantly greater inhibition of histamine-induced flares than did desloratadine at 2–6 hours after treatment ($p \leq 0.005$) and a significantly greater mean percent reduction from baseline in flares at 2 hours (61% versus +2%, respectively), 3 hours (83% versus 18%), 4 hours (79% versus 3%), 5 hours (75% versus 27%), and 6 hours (85% versus 36%) after treatment ($p < 0.05$).²⁹ Fexofenadine also produced significantly greater inhibition of histamine-induced wheals than did desloratadine at 2–4 hours, 6–9 hours, and at 12 hours after treatment ($p < 0.05$); additionally, a trend toward improved wheal inhibition was observed with fexofenadine at 5 hours after treatment ($p = 0.05$). Plasma concentrations of the two drugs were not available from this study, so it was not possible to calculate the RO. However, in line with the pharmacodynamic data reported in this study, an article by Gillard *et al.*¹² showed that the RO of fexofenadine at 4 hours appears to be higher (95%) than that of desloratadine (71%; Table 3).

Effect of pH

Given that receptor affinity can vary with pH and that acidosis has been reported to be a feature of in-

Table 4 Pharmacokinetic parameters and receptor occupancy (RO) of desloratadine compared with levocetirizine in a wheal and flare study

Parameter	Desloratadine, 5 mg	Levocetirizine, 5 mg	Difference (95% CI)
Plasma elimination half-life ($t_{1/2}$), hr	27	8	—
Plasma protein binding, %	85	91	—
K_i (nM)			—
K_i (t 37 C, pH 7.4)	0.4	3.0	—
K_i (t 37 C, pH 5.8)	0.63	1.3	—
Mean (SD) free drug concentration, nM			
12 hr	0.394 (0.118)	11.3 (2.61)	—
24 hr	0.215 (0.075)	3.90 (1.59)	—
Mean (SD) RO, %, for K_i at pH 7.4			
12 hr	48.6 (7.6)	78.3 (4.4)	29.8 (25.7–33.8)*
24 hr	34.0 (7.7)	54.1 (11.7)	20.1 (14.3–25.9)*
Mean RO, % ($\pm$ SD), for K_i at pH 5.8			
12 hr	37.7 (7.0)	89.2 (2.6)	51.5 (48.0–55.0)*
24 hr	24.9 (6.4)	72.2 (10.2)	47.4 (42.3–52.4)*

Source: Adapted with permission from Ref. 28.

When evaluated at pH 7.4, a statistically significant difference of 30 and 20 between the percentages of RO by levocetirizine and desloratadine was obtained at 12 and 24 hr postdose, respectively. This difference reached 52 and 47 when RO computation was performed using the K_i values obtained at pH 5.8.

*Statistically significant ($p < 0.001$).

flammatory processes as seen in allergic reactions,³⁰ RO was calculated in acidic conditions and neutral conditions after drug intake.^{28,31} At pH 7.4, RO at 12 hours with desloratadine and levocetirizine was 49 and 78%, respectively, whereas at pH 5.8, RO at 12 hours was 38% versus 89%, respectively (Table 4).²⁸

Kinetics of Plasma Concentrations, Pharmacodynamic Effects, and RO of Levocetirizine. Estimation of the kinetics of RO can aid in evaluating data obtained in pharmacodynamic studies, as well as in establishing administration and dosing schedules of H_1 antihistamines. A study conducted in 20 healthy volunteers to calculate the kinetics of levocetirizine indicated that the percentage of RO after intake of 2.5 or 5.0 mg of levocetirizine at steady state in the interval between 0.25 and 6 hours is similar (at least 90%).³² However, between 6 and 24 hours, the percentage of RO after 2.5 mg is less than the corresponding values after 5.0 mg, being only 72–75% of those seen with 5 mg at 24 hours. These results were not unexpected, because RO is not linearly related to the concentration of a drug (see Eq. 1). Specifically, reducing a drug concentration by one-half will not decrease its RO to the same extent. However, these findings suggest that 2.5 mg of levocetirizine is active, but for a shorter period compared with 5.0 mg. The onset of RO was rapid, as the percentage of RO was 89% and 80% at 0.25 hours after the 5.0- and 2.5-mg daily dose, respectively.

If the percentages of wheal inhibition after levocetirizine intake are plotted versus the free plasma concentrations measured at the corresponding times, a counterclockwise hysteresis loop is obtained; *i.e.*, the inhibition observed at a given free plasma concentration (*e.g.*, 5 nM) is low (<10%) at a short time (5 minutes) and high ($\approx$ 60% or more) at 24 hours. However, the counterclockwise hysteresis, which is indicative of a time lag between plasma concentration and effect,^{32,33} is greatly reduced if the percentages of wheal inhibition are plotted against H_1 RO by levocetirizine.^{32,33} The possibility exists, however, that the free plasma concentrations of levocetirizine do not reflect those at the receptor in short periods and that RO percentages calculated during such periods may be overestimated; if this is the case, the hysteresis would almost disappear.

RO and Allergic Rhinitis Symptoms

A study investigating the relationship between RO and the reduction of symptoms of seasonal allergic rhinitis by levocetirizine in 119 ragweed-sensitive patients (mean age, 34 years) exposed to pollen in an environmental exposure unit illustrated the difficulty in correlating RO, free plasma concentration, and change from baseline in mean major symptoms complex score over time (Table 5).³⁴ Free plasma concen-

Table 5 Plasma concentrations, receptor occupancy (RO) and major symptoms complex (MSC) scores at different times after administration of a single 5-mg dose of levocetirizine*

Time After Administration (hr)	Mean Plasma Concentration (ng/mL)	Mean Free Plasma Concentration (nM)	Mean RO (%)	Mean MSC Score	Mean Change From Baseline# in MSC Score
0.25	124.3	24.2	89	—	—
0.5	230.3	44.9	94	17.11	0.74
1.0	230.9	45.0	94	12.18	-4.18
1.5	205.0	39.9	93	9.86	-6.51
2.0	189.1	36.8	93	8.71	-7.66
2.5	—	—	—	7.53	-8.83
3.0	168.4	32.8	92	7.24	-9.12
3.5	—	—	—	7.14	-9.22
4.0	151.1	29.4	91	7.24	-9.13
4.5	—	—	—	6.96	-9.40
5.0	—	—	—	7.20	-9.16
6.0	110.4	21.5	88	—	—
9.0	75.1	14.6	83	—	—
12.0	54.5	10.6	78	—	—
16.0	35.1	6.8	69	—	—
21.5	—	—	—	8.18	-8.17
24.0	18.4	3.6	55	8.82	-7.52

Source: Ref. 34.

*N =119.

#MSC score at baseline was 16.36.

trations of levocetirizine do not necessarily represent those at the receptor for a particular short time interval; the RO values calculated may be overestimated at these times. It is also possible that there is a lag time between the RO and the relief of some of the symptoms.

RO of Levocetirizine in Allergic Children

RO in school-aged allergic children treated with a 5-mg oral dose of levocetirizine has been shown to be similar to that in adults treated with the same dose. For example, in a study in 14 allergic children (mean age, 8.6 ± 0.6 years) treated with levocetirizine, H₁ RO at 4 and 24 hours was 94% and 60%, respectively, compared with 90% and 57%, respectively, in adults.³⁵ At 4 hours, wheal and flare suppressions were 100% and 94%, respectively, in children and 100% and 89%, respectively, in adults; at 24 hours, wheal and flare suppressions were 72% and 90%, respectively, in children and 60% and 74%, respectively, in adults.

A separate study compared results of nine children (mean age, 1.76 years) with recurrent cough and other allergy-related symptoms treated with levocetirizine, 0.125 mg/kg twice daily, and results obtained in 20 adults (mean age, 25.1 years) treated with levocetirizine, 5 mg once daily.³⁶ In the children, the elimination of levocetirizine was rapid (terminal half-life, 4.1 hours). Steady-state concentrations at peak were simi-

lar to those observed in adults, whereas steady-state concentrations at trough were higher. At steady state, 12 hours after administration of a 0.125-mg/kg dose of levocetirizine (total daily dose = 0.25 mg/kg) in the children, RO was 81%. This was consistent with the pharmacodynamic data obtained in the same study showing an inhibition of histamine-induced wheal and flare of 95% and 98%, respectively, at steady state 12 hours after administration of the 0.125-mg/kg dose.³⁷ By comparison, RO was only 50% at 24 hours after repeated administration of levocetirizine, 0.25 mg/kg, administered once daily. This favors recommending a dosing regimen of levocetirizine, 0.125 mg/kg twice daily, in children aged 1–2 years.

DISCUSSION

Antihistamines are the first-line treatment of choice for mild to moderate rhinoconjunctivitis³⁸ and chronic urticaria.³⁹ The predicted clinical efficacy of such drugs in humans is often based on receptor affinity measured *in vitro* in experimental conditions, which are very different from physiological conditions, and on the value of plasma half-life. Studies comparing the pharmacodynamics of H₁ antihistamines, however, suggest that a suitable estimation of RO (using free plasma concentrations and an affinity value obtained in conditions as close as possible to the pathophysiological

ones) may be a more reliable predictor of human pharmacodynamics than *in vitro* affinity and plasma half-life only.¹² Data support the hypothesis that the higher and more sustained potency of levocetirizine in inhibiting histamine-induced wheal and flare, compared with that of desloratadine or fexofenadine, can be explained by the higher and more sustained H₁ RO of levocetirizine. RO correlates well with inhibition of allergen-induced wheal and flare and reduction of symptoms of seasonal allergic rhinitis in patients exposed to pollen in an environmental exposure unit, a model that is a good predictor of clinical efficacy.

CONCLUSIONS

The RO model as a predictor of human pharmacodynamics and antihistamine efficacy may be a more accurate way to describe the clinical efficacy of a drug than current models because it takes into account both the affinity of the drug for the receptor and its free plasma concentration. Additional investigation is warranted to elucidate the role of RO theory in drug development and the administration and dosing of drugs in clinical practice.

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