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The concept of receptor occupancy to predict clinical efficacy: a comparison of second generation H_1 antihistamines

Key words: *allergic rhinitis, antihistamine, chronic idiopathic urticaria, desloratadine, fexofenadine, histamine H_1-antagonists, levocetirizine, receptor occupancy, treatment outcome*

The H1 antihistamines are commonly used in the treatment of allergic disorders 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. 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. Second generation H1 antihistamines were developed to minimize or alleviate such deficiencies; however, the first two of these agents (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.

The main pharmacokinetic features of the second- generation H1 antihistamines (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. 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 (absorption, distribution, metabolism, and excretion).

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 recaptor [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 response [12], localized swelling due to plasma extravasation (wheal) and a neurovascular response

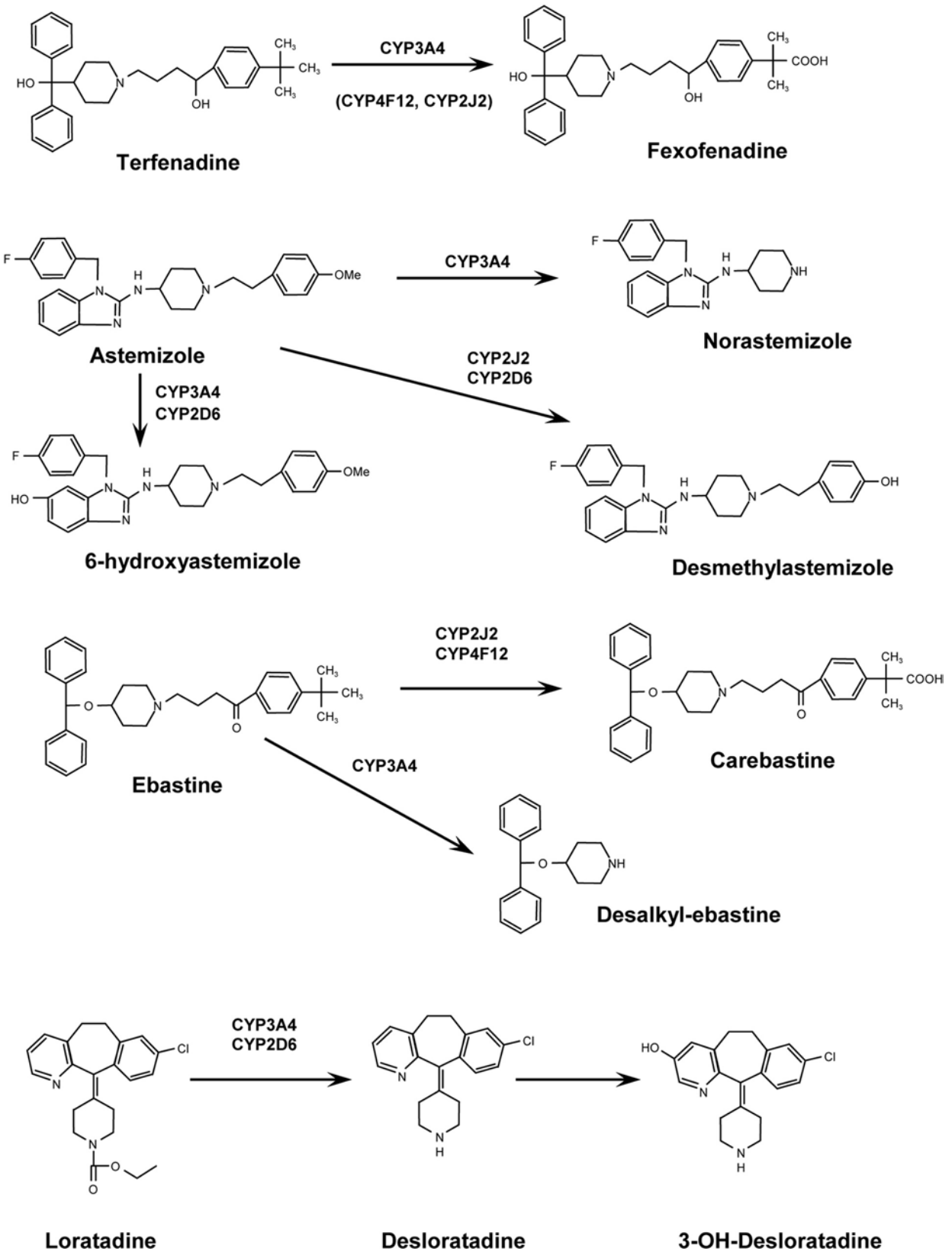

Fig. 1. **Chemical structure and basic metabolic pathways of some second-generation antihistamines**

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.

Materials and 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

Table 1

Main pharmacokinetic and metabolic features of seven nonsedating H1 antihistamine drugs

Features	Parameters	Cetirizine	Desloratadine	Ebastine (Carabastine)	Fexofenadine	Levocetirizine	Loratadine	Mizolastine
Absorption	Tmax, h	1	3	3–6	2–3	0–9	1,5	1,5
Distribution	Vz/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	(~4,3–2,0)	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

T_{rmx} = time to reach peak plasma levels of the unchanged drug; Vz/F = volume of distribution during the terminal phase/bioavailability; CYP = cytochrome P450; UGT = glucuromsyltransferase; NA = mt available.

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.

Results

Calculation of In Vivo RO

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

$$\mathrm{RO}\% = B_{\mathrm{Max}} \times \frac{[L]}{([L] + K_i)}, \qquad (1)$$

where Bmax is the maximum number of binding sites (set to 100 %), [L] – is the free concentration of drug at the receptor site, and Ki 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) [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 H1 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 (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].

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
Ki	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 pharmacologicallyactive

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 receptors [12]: 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 (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 antihista- mine 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:

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

wherein [H] is the free concentration of histamine and Kh 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]/Kh. 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 mucosa [17] and

~20 nM in skin (perfu- sates 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 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) [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 (ebastine metabolized to cerebastine, 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 paren compound in the presence of histamine:

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

wherein [M] and Km 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 volun- teers [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.

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 fexofe- nadine 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 (the elimination half-life), which can be long but with very low plasma levels if it is preceded by a short half-life (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 levocetiriz- ine, 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, patients receiving levocetirizine showed the

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,	Fexofenadine,	Levocetirizine,
	5 mg	120 mg	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

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 ($p < 0,001$), 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 deslora- tadine, 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 ($p < 0,005$) 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 inflammatory 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 H1 antihistamines. A study conducted in 20 healthy volunteers to calculate the kinetics of levocetirizine indiciated 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

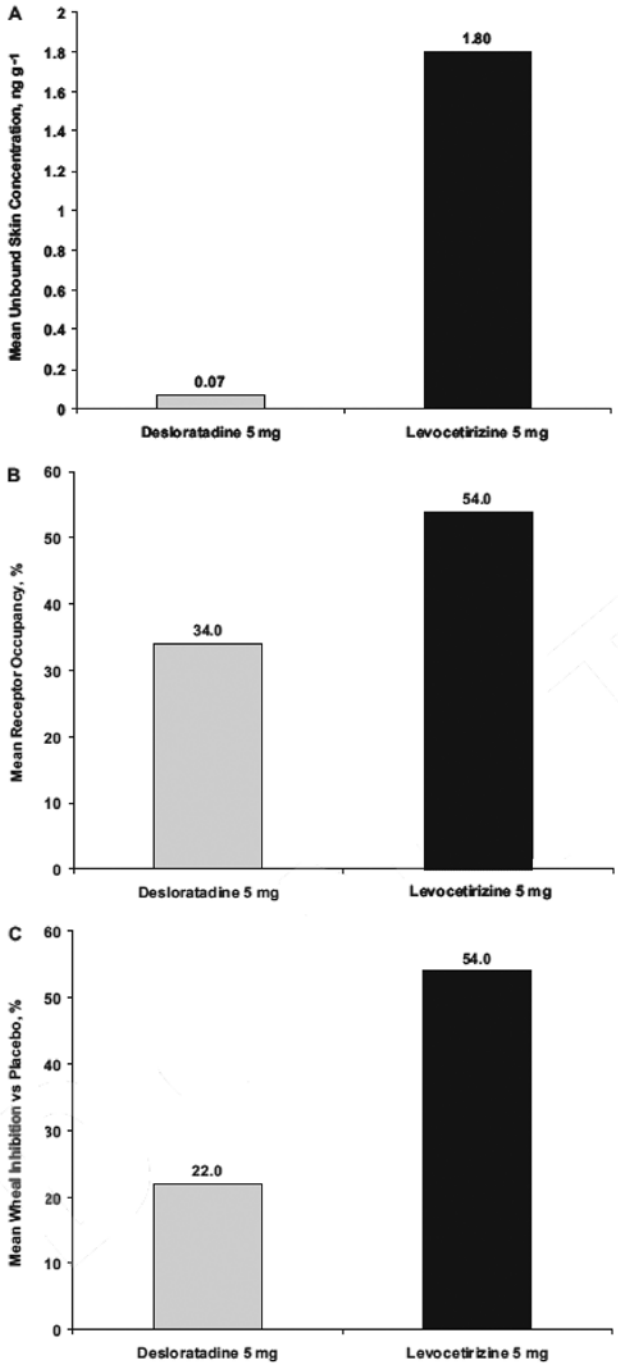

Figure 2. Shown are (A) unbound skin concentration at 24 hours after drug intake (n = 18), (B) receptor occupancy measured 24 hours after drug intake (n = 18), and (C) mean wheal inhibition at 24 hours after drug intake (n = 18). (Source: Ref. 27.)

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; the inhibition observed at a given free plasma concentration (5 nM) is low (< 10 %) at a short time (5 minutes) and high (~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 H1 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 concentrations 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 similar 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.

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

Parameter	Desloratadine,	Levocetirizine,	Difference
	5 mg	5 mg	(95 % CI)
Plasma elimination half-life (t1/2), hr	27	8	—
Plasma protein binding, %	85	91	—
Ki (nM)			—
Ki (t 37°C, pH 7,4)	0,4	3.0	—
Ki (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 Ki 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, % (±SD), for Ki 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)*

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 Ki values obtained at pH 5,8; * – Statistically significant ($p < 0.001$).

Discussion

Antihistamines are the first-line treatment of choice for mild to moderate rhinoconjunctivitis [38] 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.

References

1. *Whomsley, R.* Development of new H_1-antihistamines: The importance of pharmacokinetics in theevaluation of safe and therapeutically effective agents [Text] / R. Whomsley, M. S. Benedetti // Curr. Med. Chem. – 2005. – Vol. 4. – P. 451.

2. *Plaut, M.* and Valentine MD. Clinical practice. Allergic rhinitis [Text] / M. Plaut, M. D. Valentine // N. Engl. J. Med. – 2005. – Vol. 353. – P.1934 –1944.

3. *Zuberbier, T.* et al. EAACI/GA2LEN/EDF guideline: Management of urticaria [Text] / T. Zuberbier [et al.] // Allergy. – 2006. – Vol. 61. P. 321–331.

4. *Dykewicz, M. S.* et al. Diagnosis and management of rhinitis: Complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology [Text] / M. S. Dykewicz [et al.] // American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol. – 1998. – Vol. 81. – P. 478 –518.

5. *Molimard, M.* Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans [Text] / M. Molimard, B. Diquet, M. S. Benedetti // Fundam Clin Pharmacol. – 2004. – Vol. 18. – P. 399 –411.

6. *Paton, D. M.* Clinical pharmacokinetics of H_1-receptor antagonists (the-antihistamines) [Terxt] / D. M. Paton, D. R. Webster // Clin. Pharmacokinet. – 1985. – Vol. 10. – P. 477– 497.

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.

7. *Scheife, R. T.* Sedative and cardiovascular profile of newer-antihistamines [Text] / R. T. Scheife, W. R. Cramer // Consult. Pharm. – 1996. – Vol. 11. – P. 1037–1053.

8. *Markham, A.* Fexofenadine [Text] / A. Markham, A. J. Wagstaff // Drugs. – 1998. – Vol. 55. – P. 269 –274.

9. *Waldman, S. A.* Does potency predict clinical efficacy? Illustration through an-antihistamine model [Text] / S. A. Waldman // Ann. Allergy Asthma Immunol. – 2002. – Vol. 89. – P. 7–11.

10. *Bourne, H. R.* and von Zastrow M. Drug receptors and pharmacodynamics. In Basic and Clinical Pharmacology, 10th ed. Katzung BG (Ed). – New York : McGraw-Hill Medical, 2007. – P. 11–33.

11. *Holford, N. H. G.* Pharmacokinetics and pharmacodynamics: Rational dosing and the time course of drug action. In Basic and Clinical Pharmacology, 10th ed. Katzung BG (Ed). – New York : McGraw-Hill Medical, 2007. – P. 34 – 49.

12. *Gillard, M.* Histamine H_1-receptor occupancy and pharmacodynamics of second generation H_1-antihistamines [Text] / M. Gillard [et al.] // Inflamm Res. – 2005. – Vol. 54. – P. 367–369.

13. *Weiland, G.A.* Quantitative analysis of drugreceptor interactions: I. Determination of kinetic and equilibrium properties [Text] / G. A. Weiland, P. B. Molinoff // Life Sci. – 1981. – Vol. 29. – P. 313–330.

14. *Strolin Benedetti, M.* Estimation of receptor occupancy. When is this relevant for the efficacy of an H_1-antihistamine? [Text] / M. Strolin Benedetti [et al.] // Allergy Clin Immunol Int. – 2006.- Vol. 18. – P. 131–133.

15. *Strolin Benedetti, M.* et al. Pharmacodynamics of latest generation H_1-antihistamines: Relevance of drug concentrations at receptor sites and of affinity values for H_1-receptors [Text] / M. Strolin Benedetti [et al.] // Allergy Clin. Immunol. Int. J. World Allergy Org. – 2007. – Suppl. 2. – P. 162–166.

16. *Gillard, M.* Binding characteristics of cetirizine and levocetirizine to human H_1-histamine receptors: Contribution of Lys(191) and Thr(194) [Text] / M. Gillard [et al.] // Mol. Pharmacol. – 2002. – Vol. 61. – P. 391–399.

17. *Jokuti, A.* Histamine metabolism is altered in nasal polyposis [Text] / A. Jokuti [et al.] // Inflamm. Res. 53 (suppl. 1). – 2004. – S93–S94.

18. *Petersen, L. J.* Histamine is released in the wheal but not the flare following challenge of human skin in vivo: A microdialysis study [Text] / L. J. Petersen [et al.] // Clin. Exp. Allergy. – 1997. – Vol. 27. P. 284 – 295.

19. *Halmerbauer, G.* In vivo histamine release during the first minutes after deliberate sting challenges correlates with the severity of allergic symptoms [Text] / G. Halmerbauer [et al.] // Pediatr. Allergy Immunol. – 1999. – Vol. 10. – P. 53–57.

20. *Venza, I.* Quantitative determination of histamine in tears during conjunctivitis by a novel HPLC method [Text] / I. Venza [et al.] // Ophthalmic. Res. – 2004. – Vol. 36. – P. 62– 69.

21. *Pawankar, R.* Mast cells in allergic airway disease and chronic Rhinosinusitis [Text] / R. Pawankar // Chem. Immunol. Allergy. – 2005. – Vol. 87. P. 111–129.

22. *Simons, K.* Hydroxyzine and its active metabolite cetirizine: H_1-receptor occupancy in healthy elderly adults [Text] / K. Simons [et al.] // Allergy 63 (suppl. 88). – 2008. – 541 (Abs 1495).

23. *Tashiro, M.* Central effects of fexofenadine and cetirizine: Measurement of psychomotor performance, subjective sleepiness, and brain histamine H_1-receptor occupancy using 11C-doxepin positron emission tomography [Text] / M. Tashiro [et al.] // J. Clin. Pharmacol. – 2004. – Vol.44. – P. 890 –900.

24. *Tashiro, M.* Brain histamine H_1-receptor occupancy of orally administered-antihistamines measured by positron emission tomography with (11)C-doxepin in a placebo-controlled crossover study design in healthy subjects: A comparison of olopatadine and ketotifen [Text] / M. Tashiro [et al.] // Br. J. Clin. Pharmacol. – 2005. – Vol. 61. P. 16 –26.

25. *Strolin Benedetti, M.* Histamine H_1-receptor occupancy following single and repeated administration of H_1-antihistamines [Text] / M. Strolin Benedetti [et al.] // Presented at the 25th Congress of the European Academy of Allergology and Clinical Immunology. – Vienna, Austria, June 10 –14, 2006 (Abs 1454).

26. *Strolin Benedetti, M.* Histamine H_1-receptor occupancy by levocetirizine and fexofenadine in allergic rhinitis and chronic idiopathic urticaria [Text] / M. Strolin Benedetti [et al.] // Presented at the 26th EEACI Congress, Göteborg, Sweden, June 9 –13, 2007 (Abs 76247).

27. *Frossard, N.* et al. Inhibition of allergen-induced wheal and flare reactions by levocetirizine and desloratadine [Text] / N. Frossard [et al.] // Br. J. Clin. Pharmacol. – 2008. – Vol. 65. – P. 172–179.

28. *Strolin Benedetti, M.* Evaluation of the receptor occupancy by desloratadine and levocetirizine in allergic subjects [Text] / M. Strolin Benedetti. [et al.] // World Allergy Org. J. – 2007 (Abs 514). – S163–S164.

29. *Meltzer, E. O.* Efficacy of fexofenadine versus desloratadine in suppressing histamine-induced wheal and flare [Text] / E. O. Meltzer, S. A. Gillman // Allergy Asthma Proc. – 2007. – Vol. 28. – P. 67–73.

30. *Vermeulen, M. E.* The impact of extracellular acidosis on dendritic cell function [Text] / M. E. Vermeulen [et al.] // Crit. Rev. Immunol. – 2004. – Vol. 24. – P. 363–384.

31. *Gillard, M.* Changes in pH differently affect the binding properties of histamine H_1 receptor antagonists [Text] / M. Gillard, P. Chatelain // Eur. J. Pharmacol. – 2006. – Vol. 20. – P. 205–514.

32. *Strolin Benedetti, M.* The degree of receptor occupancy in the interpretation of the pharmacodynamics of levocetirizine [Text] / M. Strolin Benedetti [et al.] // Presented at the XXVIth Congress of the European Academy of Allergology and Clinical Immunology. – Goteborg, Sweden, , 2007, June 9 –13.

33. *Tighe, K. E.* Persistently high plasma morphine-6-glucuronide levels despite decreased hourly patient-controlled analgesia morphine use after single-dose diclofenac: Potential for opioid-related toxicity [Text] / K. E. Tighe [et al.] // Anesth. Analg. – 1999. – Vol. 88. – P. 1137–1142.

34. *Strolin Benedetti, M.* Relationship between histamine H_1 receptor occupancy (RO) and reduction of symptoms of seasonal allergic rhinitis (SAR) by levocetirizine (L) in subjects exposed to pollen in an environmental exposure unit (EEU). [Text] / M. Strolin Benedetti [et al.] // Presented at the 20th World Allergy Congress. – Bangkok, Thailand, 2007, December 2– 6 (Poster 252).

35. *Simons, K. J.* Levocetirizine: H_1-receptor occupancy in allergic children age 6 –11 years [Text] / K. J. Simons [et al.] // Poster Presented at the 62nd Annual American Academy of Allergy, Asthma and Immunology Meeting. – Miami Beach, FL, 2006, March 3–7.

36. *Le Lamer, S.* Pharmacokinetics of levocetirizine in children of 1–2 years and rationale for dosing regimen [Text] /S. Le Lamer, M. Strolin Benedetti // Allergy 62 (Suppl 83). – 2007. – P. 306 –307.

37. *Cranswick, N.* Levocetirizine in 1–2 year old children: Pharmacokinetic and pharmacodynamic profile [Text] / N. Cranswick [et al.] // Int. J. Clin. Pharmacol. Ther. – 2005. – Vol. 43. – P. 172–177.

38. *Bousquet, J.* Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen) [Text] / J. Bousquet [et al.] // Allergy. – 2008. – 63 (suppl. 86):8 –P. 160.

39. *Powell, R. J.* BSACI guidelines for the management of chronic urticaria and angio-oedema [Text] / R. J. Powell [et al.] // Clin. Exp. Allergy. – 2007. – Vol. 37. – P. 631– 650.

THE CONCEPT OF RECEPTOR OCCUPANCY TO PREDICT CLINICAL EFFICACY: A COMPARISON OF SECOND GENERATION H_1-ANTIHISTAMINES

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Summary

Second generation H_1-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 efficacyof 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 H_1-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.

Key words: *Allergic rhinitis, antihistamine, chronic idiopathic urticaria, desloratadine, fexofenadine, histamine H_1-antagonists, levocetirizine, receptor occupancy, treatment outcome*

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КОНЦЕПЦІЯ ЗАМІЩЕННЯ РЕЦЕПТОРІВ ЯК ПРЕДИКТОР КЛІНІЧНОЇ ЕФЕКТИВНОСТІ ПРЕПАРАТУ: ПОРІВНЯЛЬНИЙ АНАЛІЗ БЛОКАТОРІВ H_1-РЕЦЕПТОРІВ ДРУГОГО ПОКОЛІННЯ

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Резюме

Антигістамінні препарати другого покоління є терапією першої лінії в лікуванні хронічного риніту та хронічної ідіопатичної кропивниці. Велике значення має оцінка фармакокінетичних та фармакодинамічних властивостей препаратів та їх клінічної ефективності, але точні моделі для прогнозування останньої на даний момент відсутні. Показник ступеня заміщення рецепторів є предиктором фармакодинаміки та антигістамінного потенціалу препарату, відбиває його спорідненість до рецепторів та плазмову концентрацію. Таким чином, заміщення рецепторів може розглядатися як більш точний показник клінічної ефективності препарату. Дане дослідження було проведено з метою вивчення кореляції показника заміщення рецепторів та клінічної ефективності препарату на прикладі антигістамінних препаратів другого покоління. Огляд літератури проводився з використанням MEDLINE. Пошук здійснювався по термінах: алергія, алергічний риніт, ефективність лікарського засобу, патентовані лікарські засоби, багаторічний алергічний риніт, сезонний алергічний риніт, друге покоління антигістамінних препаратів, хронічна ідіопатична кропивниця, результати лікування.

Також було використано тези та інформаційні матеріали останніх з'їздів та конференцій на тему алергії.

Показник заміщення рецепторів для кількох антигістамінних препаратів другого покоління було отримано в порівняльних дослідженнях. Показник заміщення рецепторів у фексофенадину та левоцетиризіну був вище в перші 4 години після прийому порівняно з дезлоратадином. Даний показник залишався вищим у левоцетиризіну через 12 та 24 годин порівняно з фексофенадином і дезлоратадином. Показник заміщення рецепторів цих препаратів корелював з показниками фармакодинаміки, такими як шкірні та загальні прояви алергії. На показник заміщення рецепторів впливає час від моменту останнього прийому препарату, pH і режим дозування. Між заміщенням рецепторів і концентрацією препарату в плазмі крові визначається нелінійна залежність. Результати дослідження вказують, що RO є точним предиктором фармакодинамічної активності та клінічної ефективності in vivo.

Ключові слова: *алергічний риніт, антигістамінні препарати, хронічна ідіопатична кропивниця, дезлоратадин, фексофенадин, гістамин, H_1-антагоністи, левоцетиризін, ступінь заміщення рецепторів, результати лікування.*

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