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New antihistamines: a critical view

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Abstract

Objective: To perform a critical evaluation of the more recent H1 antihistamines and the various terms used to describe them, based on a review of evidence on their role in the treatment of allergic disorders.

Sources: Original articles, reviews and consensus documents published from 1998 to 2006 and indexed in the MEDLINE and PubMed databases. Keyword: antihistamines.

Summary of the findings: Second-generation antihistamines differ from first-generation ones because of their elevated specificity and affinity for peripheral H1 receptors and because of their lower penetration of the central nervous system (CNS), having fewer sedative effects as a result. Whilst second-generation antihistamines are in general better tolerated than their predecessors, some adverse effects, principally cardiotoxicity, have been observed with some of them. Over the last 20 years, new compounds with different pharmacokinetic properties have been synthesized. The majority of these exhibit anti-inflammatory properties that are independent of their action on the H1 receptor. More recent improvements, generally in the form of active metabolites, led to the use of the term third-generation antihistamines. This term emerged spontaneously, with no clear definition of its meaning or clinical implications, creating great confusion among healthcare professionals.

Conclusions: On the basis of the evidence on H1 antihistamines, none of them deserve the title "third-generation antihistamine." As the Consensus Group on New Generation Antihistamines concluded, to merit this definition, a new class of antihistamines would have to demonstrate distinct clinical advantages over existing compounds and fulfill at least three prerequisites: they should be free from cardiotoxicity, drug interactions and effects on the CNS.

J Pediatr (Rio J). 2006;82(5 Suppl):S173-80: Antihistamines, desloratadine, fexofenadine, levocetirizine, rupatadine.

Introduction

Several different mediators are involved in the pathophysiology of allergic diseases. Despite this, histamine remains the principal one, and plays a fundamental role in the genesis of these diseases, particularly rhinitis and urticaria. Produced and stored within the cytoplasmic granules of mast cells and basophils, histamine is already liberated in large quantities during the immediate phase of allergic reactions.[1]

To date four subtypes of histamine receptors have been described (H1, H2, H3 and H4). They all belong to the superfamily of G protein-coupled receptors[2] and differ in terms of location, secondary messengers and histamine-binding properties.[3] Histamine exerts its effects in allergic diseases primarily interacting with H1 receptors present in a variety of organs.

In the nose histamine stimulates the sensory nerve endings (itching and sneezing), increases vascular permeability (edema and obstruction) and glandular secretions (rhinorrhea). In the skin it provokes vasodilation and increase in vascular permeability (erythema and edema) and stimulates sensory nerve endings (itching). In the lungs it primarily acts on the bronchial smooth muscle (bronchoconstriction).[1,4]

Chronically, histamine has effects on inflammatory cells and causes cellular activation (mast cells, basophils and eosinophils) and release of proinflammatory mediators (for example, leukotrienes and cytokines); and increases in the expression of class II human histocompatibility molecules (HLA) and vascular endothelial adhesion molecules.[5,6]

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Antihistamines

Antihistamines are described according to the histamine receptor with which they interact. Thus, those that have a predilection for H1 receptors, H2, H3 and H4 are called, H1 antihistamines, H2 antihistamines, H3 antihistamines and H4 antihistamines, respectively. It is H1 antihistamines that are most often used for treating allergic disorders.

Mechanisms of action of H1 antihistamines: treatment rationale

H1 antihistamines are among the most prescribed medications in the world and, although they have similar efficacy for the treatment of patients with allergic rhinoconjunctivitis, urticaria and other allergic diseases, they differ significantly in terms of their chemical structure, clinical pharmacology and toxicity potential.[7] Depending on their action on the central nervous system (CNS), they are classified as "classic", or first-generation, and "non-classic", or second-generation.

In general, first-generation H1 antihistamines (for example, dexchlorpheniramine and hydroxyzine) are rapidly absorbed and metabolized, which means they must be administered three or four times a day. Since they have reduced molecular structures and are highly lipophilic, they cross the blood-brain barrier (BBB), bind with ease to the cerebral H1 receptors and thereby create their principal side-effect: sedation.[5]

Over the last 20 years, second-generation H1 antihistamines were synthesized– compounds with high potency, long-lasting effect and minimal adverse effects. They are unlikely to cross the BBB and rarely cause sedation.[5] In Brazil the following are available for oral use: cetirizine, ebastine, epinastine, fexofenadine, loratadine, desloratadine, levocetirizine and rupatadine. As a result of their high-affinity for the H1 receptors, they have a prolonged half-life, which means they need only be taken once or twice a day.

Effects on the H1 receptor

For years it was believed that H1 antihistamines acted as competitive histamine antagonists, blocking the site where histamine binds with receptors. Recently it became clear that there are two H1 receptor isoforms, an active and an inactive form, which are in equilibrium on cell surfaces.[2] It was realized that the receptors have "agonist-independent" signal transduction, in other words, even in the absence of histamine they are constitutively in the "on" position - activate. Therefore, it is believed that H1 antihistamines inhibit this constitutive signal and stabilize the receptor's inactive configuration, acting, therefore, as inverse agonists and not as antagonists.[2]

Traditionally, the efficacy of H1 antihistamines for treatment of allergic diseases has been primarily attributed to their capacity to downregulate the activity of histamine on H1 receptors located on endothelial cells, airway smooth muscle and sensory nerve endings. Thus they are capable of a) reducing vascular permeability, vasodilation and glandular secretion, improving rhinorrhea, erythema and cutaneous edema; b) promote bronchodilation; and c) reduce sneezing and itching of nasal mucosa and skin.[1]

Antiallergic/anti-inflammatory effects

Originally, studies of the relative potencies of H1 antihistamines were based on the capacity of different compounds to competitively inhibit the H1 receptor binding of histamine, i.e. on their blocking effect on the receptor.[8] Nevertheless, it has already been known for some time that, in addition to acting on H1 receptors, many H1 antihistamines, at appropriate doses, are capable of inhibiting not only the release of histamine by mast cells,[9,10] but also mast cell activation itself.[11] Some of them can even regulate the expression and/or release of cytokines, chemokines, adhesion molecules and inflammatory mediators.[5,8]

Therefore, the antiallergic properties of H1 antihistamines are generally a reflection of their capacity to affect mast cell and basophil activity, inhibiting the release of preformed mediators such as histamine, tryptase, leukotrienes and others.[8] Several second-generation H1 antihistamines have demonstrated antiallergic properties, irrespective of their interaction with the H1 receptor.[5,8]

Chronic allergic inflammation resulting from the late-phase reaction, exhibits components that are similar to other forms of inflammation, including chemotaxis of inflammatory cells followed by activation and proliferation, with subsequent production and release of many chemical mediators. Among cells involved in allergic inflammation are: antigen-presenting cells (for example, macrophages), mast cells, basophils, T lymphocytes, epithelial/endothelial cells and eosinophils – major effectors of chronic inflammation. Cytokines, chemokines, inflammatory mediators and adhesion molecules also contribute to this process which ultimately leads to dysfunction of the affected organ.[8]

Many second-generation H1 antihistamines (particularly cetirizine) are capable of inhibiting the influx of eosinophils to the site of allergen challenge in sensitized individuals.[5,8] Studies have demonstrated that some of them can also alter adhesion molecules expression on epithelium and eosinophils, and reduce *in vitro* survival of eosinophils. Finally, some second-generation H1 antihistamines are capable, *in vitro* and *in vivo*, of altering the production of inflammatory cytokines (for example, TNF-α, IL-1ß and

IL-6) and the Th1/Th2 balance regulation cytokines (for example, IL-4 and IL-13).[5,8]

Therefore, it is well established that, in addition to their effects on H1 receptors, many second-generation H1 antihistamines also manifest antiallergic and anti-inflammatory properties which differ depending upon their molecules and the experiments used for their evaluation.[5]

Clinical and pharmacological effects

The scientific basis for the use of antihistamines with maximum efficacy in all types of patients (young, elderly, patients with hepatic or renal dysfunction or on other medication) is documented in pharmacokinetic and pharmacodynamic studies.[7] Clinical efficacy in humans does not only depend on the potency and specificity of the H1 antihistamine, but also on its concentration at the receptor site.[1]

Second-generation H1 antihistamines have high affinity and selectivity for the H1 receptor. After oral administration at usual dosages, they rapidly achieve peak concentration in tissues.[1,7] The majority of them begin to act 1 to 2 hours after administration, with effects manifest for 24 hours, and so can be taken once a day.[7]

Their activity does not diminish with regular, daily use for prolonged periods. These compounds maintain the capacity both to suppress the wheal and flare induced by histamine and to control the symptoms of persistent allergic rhinitis and chronic urticaria, for weeks and months.[1]

In patients with allergic rhinitis (AR), H1 antihistamines improve itching, sneezing and watery rhinorrhea. However, they are not so useful for controlling nasal obstruction. When administered orally, they exert their effect, not only on nasal symptoms, but also on ocular symptoms, which are frequently associated with AR.[5]

Evidence shows that continual use is of greater advantage and more effective than an on-demand regimen.[5] In children, treatment for prolonged periods can even improve lower airway symptoms[12] and have a prophylactic effect on asthma onset in monosensitized infants (to dust mites or grass pollen).[13]

Since H1 antihistamines are often prescribed for prolonged periods, the possibility that they may interact with other drugs should always be taken into consideration. All second-generation H1 antihistamines, with the exception of cetirizine, levocetirizine and fexofenadine, are metabolized via the cytochrome system. The P4503A (CYP3A) cytochrome, is known to be involved in the metabolism of many drugs used on humans. Drug interactions causing enzymatic inhibition or induction are common after the coadministration of two or more CYP3A substrates.[5]

Therefore, the administration of H1 antihistamines that are metabolized via the P450 cytochrome, in association with other drugs that employ the same route (for example, ketoconazole and erythromycin), increases the risk of adverse reactions.[5]

Side effects of H1 antihistamines

Central nervous system

H1 receptors can be found widely distributed throughout the CNS and, although their physiological role in these locations is not yet fully understood, H1 antihistamines can cause several effects within the CNS, namely: a) sedation, varying from mild somnolence to deep sleep; b) depression, identified by symptoms such as coordination disturbance, dizziness, lassitude and lack of concentration; and c) agitation.[5]

An important determinant of the occurrence of CNS side effects is the greater or lesser capacity a compound has to cross the BBB. Crossing the BBB basically depends on the existence of an active transport mechanism for the H1 antihistamine and on certain of its chemical properties, such as its lipophilicity and molecular weight. Furthermore, there is an important correlation between the sedation caused by an H1 antihistamine and its degree of affinity for the H1 receptors in the CNS.[5]

First-generation H1 antihistamines are highly liposoluble, they have low molecular weight and a high degree of affinity for cerebral H1 receptors, which means that sedation occurs with frequency, even at therapeutic doses. Second-generation H1 antihistamines, in contrast, have greater molecular weight, low liposolubility and low affinity for cerebral H1 receptors. Therefore, the majority of compounds in this generation, at therapeutic doses, are apparently devoid of significant side effects on the CNS.[5,14]

Cardiac effects

One important precaution that must be taken with H1 antihistamines relates to their potential for cardiotoxicity. These cardiotoxic effects are apparently dose-dependent, which is an extremely important fact with relation to drugs metabolized by the P450 cytochrome, since concurrent administration of compounds that compete for the same enzyme may reduce the rate at which the H1 antihistamine is metabolized, increasing its concentration in plasma.[5]

During the last 20 years adverse cardiac effects were reported (torsades de pointes, arrhythmia, prolongation of the QTc interval) with two second-generation H1 antihistamines: astemizole and terfenadine.[5,15] In these cases the compounds were invariably being administrated at doses above the recommended levels, or in association with drugs that use the same hepatic metabolism route (ketoconazole, erythromycin). It is important to point out

that these effects are not drug class-specific, but are limited to terfenadine and astemizole, which were withdrawn from the market in many countries,[5] including Brazil.

Cetirizine,[16] fexofenadine[17,18] and levocetirizine,[19,20] are minimally metabolized and so are safer.

Others

The majority of first-generation H1 antihistamines, if not all of them, exhibit pharmacological effects that are not related to their binding with H1 receptors. The principal of these is the anticholinergic effect, resulting from their capacity to bind to muscarinic receptors, causing dry mouth, tachycardia and urinary retention.[5] These effects have not been reported with second-generation H1 antihistamines.[5]

More recent antihistamines

Desloratadine

Desloratadine (DL) is an active metabolite of loratadine which has a high affinity for binding with H1 receptors. Despite this, it also interacts with the five subtypes of muscarinic receptors, which suggests that it has less selectivity for the H1 receptor when compared with other H1 antihistamines of the same generation.[21]

After oral administration, DL is rapidly absorbed and is metabolized on its first passage through the liver via the P450 cytochrome. Although this would imply a potential for interaction with other drugs that are metabolized via the same route (for example, erythromycin and ketoconazole), there is no direct evidence that this does actually take place.[22,23] As a result of its pharmacokinetic and pharmacodynamic characteristics, its effects are long-lasting and it can be taken just once a day.

Studies of the action of DL in skin have demonstrated that it has a potent suppressive effect on histamine-induced wheal and flare.[24,25] In patients with AR subjected to nasal challenge, DL promoted significant improvement in nasal flow and symptom score, when compared with a placebo.[26-28]

Antiallergic and anti-inflammatory effects have been described *in vitro*[29] and *in vivo*.[30] Double-blind, placebo-controlled trials, with adults and children over 12 years old, indicate that DL (5 mg/day) is effective for the treatment of seasonal AR,[26,31] perennial AR[32] and intermittent AR,[33] improving all nasal symptoms including obstruction,[31,32] associated non-nasal symptoms[32] and quality of life.[31] In multicenter, randomized, double-blind, placebo-controlled trials undertaken with adults with chronic idiopathic urticaria, DL (5 mg/day) was able to improve, to a significant extent, patients' symptoms and their quality of life.[34,35]

Desloratadine was shown to be safe and effective for the treatment of AR and chronic idiopathic urticaria in children aged 2 to 5 years and 6 to 11 years at dosages of 1.25 mg and 2.5 mg, respectively.[36] This is a well-tolerated compound, with a minimal incidence of adverse effects that is comparable with placebo.[31-33,36]

Desloratadine does not induce clinically relevant alterations to the QTc interval,[34,36] even in individuals given drugs that employ the same hepatic metabolism route.[22,23] Despite its potential for interaction with muscarinic receptors, no significant anticholinergic effects have been reported.[37] Compared with placebo, DL does not produce significant sedation, nor any marked effect on cognitive or psychomotor functions in healthy volunteers,[38] or patients with seasonal AR.[39]

Fexofenadine

Fexofenadine (FEX), the pharmacologically active metabolite of terfenadine, exhibits high affinity and selectivity for peripheral H1 receptors. It does not cross the BBB, is minimally metabolized and its pharmacokinetic properties allow it to be taken in a single daily dose.[5,40,41]

In models constructed to evaluate its action in skin, FEX revealed a potent suppressive effect over histamine-induced wheal and flare.[9,10,42] In patients with AR subjected to nasal challenge it promoted significant improvement in nasal flow and symptom score, when compared with a placebo.[28]

Antiallergic and anti-inflammatory effects have been described *in vitro*.[43] Double-blind, placebo-controlled clinical trials indicate that, in adults, FEX, at doses of 120 to 180 mg/day, is effective for the treatment of seasonal and perennial AR, improving all nasal symptoms, including obstruction[44,45] and also associated ocular symptoms.[44] In children aged 6 to 11 years, the same efficacy was demonstrated using FEX at 60 mg/day for seasonal and perennial AR.[46,47] Compared with placebo, FEX (120 or 180 mg/day) significantly improved quality of life and reduced the impairment of performance at work and during daily activities that is frequently associated with the symptoms of AR.[48]

Multicenter, randomized, double-blind, placebo-controlled studies have demonstrated that FEX at 120-180 mg/day is capable of significantly improving the symptoms[49,50] and quality of life of patients with chronic idiopathic urticaria.[49] Evidence indicates that FEX is safe and well-tolerated,[44-47,50] even at doses up to 11 times the therapeutic dose.[40] It is devoid of clinically significant anticholinergic effects.[51]

No other H1 antihistamine has been studied as much as FEX to investigate potential cardiotoxic effects. Its cardiovascular safety has been convincingly demonstrated at many different dosages, administered at differing

intervals, in isolation or in association with other potentially cardiotoxic drugs.[17,18]

With relation to its effect on the CNS, when compared with placebo FEX did not cause any significant adverse effect whatsoever on the cognitive or psychomotor functions of healthy volunteers.[14,52] Similarly, the frequency of sedation was comparable with that observed with placebo.[41]

Levocetirizine

Levocetirizine (LEV) is the active R-enantiomer of cetirizine. It has high selectivity and affinity for H1 receptors – around twice as great as the affinity of cetirizine. Its is rapidly and extensively absorbed, and minimally metabolized. Its pharmacological properties guarantee prolonged effect and it can be given once a day.[19,20]

Levocetirizine has a potent suppressive effect on histamine-induced wheal and flare.[10,24,25] In patients with AR subjected to nasal challenge, DL promoted significant improvement in nasal flow and symptom score, when compared with a placebo.[26-28]

Antiallergic and anti-inflammatory effects have been described *in vitro* and *in vivo*.[26,53]

Results of double-blind, placebo-controlled trials, indicate that LEV (5 mg/day) is effective for the treatment of seasonal and persistent AR in adults and children from 6 to 12 years, improving all nasal symptoms including obstruction.[26,54-56]

A meta-analysis demonstrated that LEV exhibits a consistent effect on nasal obstruction within the first hours after administration, maintaining this for 6 weeks.[57] Additionally, LEV has been shown effective in adults for the treatment of chronic idiopathic urticaria[58,59] and for the prevention of immediate and late symptoms resulting from insect bites, particularly in patients with more intense reactions.[60]

Levocetirizine does not interact significantly with any of the muscarinic receptor subtypes and, does not therefore manifest marked anticholinergic effects. This is a safe and well-tolerated compound, with a minimum incidence of adverse effects, which are comparable to placebo[55,56,58] and other active treatments.[61]

When compared with placebo, LEV does not cause sedation or any other deleterious effects on the cognition and psychomotricity of healthy volunteers.[62] In patients with persistent AR and chronic idiopathic urticaria, LEV significantly improved quality of life[58,63] and reduced the cost of prolonged treatment.[63]

Rupatadine

Rupatadine (RUP) is an H1 antihistamine that is capable of interacting both with H1 receptors and with receptors for platelet activation factor (PAF), therefore exerting an H1 antihistamine and an anti-PAF effect. It has a rapid onset of action and its effect is long-lasting, and it can be a administrated once a day.[64]

A study using a cutaneous model demonstrated that RUP has a potent peripheral H1 antihistamine effect, suppressing histamine-induced wheal and flare, in a dose-dependent manner.[65] Antiallergic and anti-inflammatory effects have been described *in vitro*.[66]

Randomized and controlled studies indicate that RUP (10 mg/day) if effective for the treatment of AR from 12 years of age on, improving the score of nasal symptoms (including obstruction) and non-nasal symptoms.[67,68] This is a safe and well-tolerated compound, with a minimal incidence of adverse effects, comparable with placebo[68] and other active treatments.[67]

At the recommended dose (10 mg/day), when compared to placebo, it does not produce any significant adverse effect whatsoever on the cognitive or psychomotor function of healthy volunteers.[65] Similarly, the frequency of sedation with RUP was similar to that observed with placebo.[68] Finally, no clinically significant increases in QTc interval were observed, even in the elderly and patients on erythromycin and ketoconazole.[64]

It is worth mentioning that, although clinically significant events have not been reported when RUP has been used in association with other drugs that use the P450 cytochrome route (erythromycin and ketoconazole), this type of association should be avoided since RUP is metabolized hepatically.[64]

Third-generation antihistamines

H1 antihistamines are highly effective at controlling many allergic disorders, in particular rhinitis and urticaria. Adverse effects associated with the use of first-generation H1 antihistamines stimulated the search for compounds that would be more effective and better tolerated – giving rise to second-generation H1 antihistamines.

Although they offer better therapeutic index, other adverse reactions came to be related to certain second-generation H1 antihistamines, notably cardiotoxicity (terfenadine and astemizole). Later refinements led to the synthesis of other compounds, many of them in the form of active metabolites. At this point the term "third-generation" began to appear in the literature to describe certain H1 antihistamines - a fact which became evident during this review.

Apparently this term - "third-generation" - arose spontaneously, with no clear definition or description of its meaning, which, undoubtedly created much confusion, both among general practitioners and among specialists. Faced with this fact, scientists and clinicians uninvolved with the pharmaceutical industry came together and

formed a Consensus Group on New Generation Antihistamines (CONGA) which analyzed several critical points, resulting in recommendations on the minimum criteria that would have to be met for H1 antihistamines could be reclassified and one could speak of a "new class or generation of H1 antihistamine".[6] Some of the main recommendations made by the CONGA are summed up below.

Anti-inflammatory properties

To date it has not been possible to establish whether the antiallergic/anti-inflammatory properties described in many experimental models do in fact exist, and, if so, what their true clinical significance is. These properties must be demonstrated *in vivo*, in humans, at therapeutic doses and under natural allergen exposure conditions.

For an H1 antihistamine to truly have antiallergic/anti-inflammatory properties it must manifest, in humans, superior efficacy to other therapies with the same properties (for example, corticosteroids). Since the greatest expression of allergic chronic inflammation is nasal obstruction, these anti-inflammatory properties must address this in a quantifiable manner. This must be demonstrated, in particular, in persistent AR, in which obstruction predominates over the other histamine-induced symptoms.

Potency, efficacy and effectiveness

The therapeutic index of an H1 antihistamine, defined as the risk-benefit relationship, is more important than its potency (determined in preclinical trials) or its efficacy (determined in clinical trials). In this sense, second-generation H1 antihistamines have more favorable therapeutic indices than the first generation ones, however none of them merit the designation "third-generation H1 antihistamine". It is probable that a true third-generation H1 antihistamine will differ radically from existing compounds.

Absence of cardiotoxicity

Adverse cardiac effects, with risk of life (QT prolongation and torsades de pointes), were described with some second-generation H1 antihistamine (terfenadine and astemizole). These effects are the result of a direct block to a specific class of potassium channels which control the cardiac repolarization phase, and are not related to the blockade of the H1 receptor. Therefore, cardiotoxicity is not a class-specific effect.

Several different pharmacokinetic and pharmacodynamic properties may precipitate an episode of arrhythmia. Therefore, physicians using H1 antihistamines should be aware of these properties, in order to avoid exposing their patients to potentially dangerous effects.

Absence of cardiotoxic effects, a characteristic that is already present in certain second-generation H1 antihistamines, must be maintained in the development of new compounds. Preclinical and clinical trials investigating their potential to cause such effects should be performed before new molecules are released onto the market.

Drug interactions

The possibility of drug interactions should never be forgotten, primarily because H1 antihistamines are commonly employed for prolonged periods. Based on this, for an H1 antihistamine to be considered third-generation, it must not: a) affect the function of any of the cytochrome P 450 via enzymes; b) displace medications bonded to plasma proteins; or c) affect active transport mechanisms that are extremely important to the absorption and excretion of drugs.

Lack of CNS effects

Three factors establish the criteria for determining the nonsedative properties of an H1 antihistamine: a) incidence of subjective somnolence; b) the objective effect on cognitive and psychomotor functions; and c) quantification of H1 receptor occupation using positronic tomography. While the last two are particularly important, all three factors must be met to a minimum acceptable level before any new H1 antihistamine can be classed as a nonsedative drug.

Final comments

Although H1 antihistamines are useful for the treatment of allergic disorders, differences that are probably related to their pharmacokinetic, pharmacodynamic, antiallergic and anti-inflammatory properties mean that the many different compounds in existence are not equally effective for the control of symptoms of the skin, nose and lungs. Furthermore, not all patients respond in the same manner to all H1 antihistamines, and those who do not benefit from one compound may respond satisfactorily to another.

Their antiallergic and anti-inflammatory effects, together with the improved safety profile, make second-generation antihistamines important elements for continuous, long term regulation of both immediate and late phase allergic reactions. However, it would be premature to reclassify H1 antihistamines on the basis of available evidence, since the diverse facets of these medications have not yet been completely investigated and their relative contribution to the global efficacy of treatment for allergic disorders remains unknown.

Antihistamines act by biding with the H1 histamine receptors. Recent advances, after the gene that codes for the H1 receptor had been cloned, improved understanding of the interactions between the ligand and the receptor on the molecular level. There is evidence that H1 antihistamines may bind to the receptor in different ways in the third and fifth transmembrane domains, depending upon specific amino acid residues. Furthermore, differences in expression of the receptor or in the microenvironment around it may determine different signal paths to be activated after exposure to histamine. Evidence has been found that all the H1 antihistamines available act more like inverse agonists than like antagonists.[6]

Thus, with the cloning of the genes that code for the histamine H1 receptor, a new area has opened up in histamine research, increasing the chances that new H1 antihistamines will be developed with greater potency, safety and selectivity.

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