# Histamine, histamine receptors and antihistamines: new concepts

## Histamina, receptores de histamina e anti-histamínicos: novos conceitos

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**Abstract:** Drugs with antihistamine action are the most commonly prescribed medication in daily dermatologic practice, both to adults and children. This article addresses new concepts of the role of histamine receptors (H1 receptors) and discusses the anti-inflammatory effects of these drugs. Second generation antihistamines differs from first generation because of their high specificity and affinity for peripheral H1-receptors. Second generation antihistamines are also less likely to produce sedation because they have less effect on the central nervous system. Although the efficacy of the various H1-antihistamines in the treatment of allergic patients is similar, even when comparing first- and second-generation drugs, these drugs are still very different in terms of their chemical structure, pharmacology and toxic properties. Consequently, knowledge of their pharmacokinetic and pharmacodynamic characteristics is essential for a better medical care, especially that offered to pregnant women, children, the elderly, and patients with co-morbidities.
Keywords: Histamine; Histamine H1 receptors antagonists; Histamine receptors; Histamine release; Histamine H1 antagonists, non-sedating; Receptors, histamine H1

**Resumo:** As drogas com ação anti-histamínica estão entre as medicações mais comumente prescritas na prática dermatológica diária, tanto em adultos como em crianças. Este artigo aborda os novos conceitos da função dos receptores de histamina (receptores H1) e discute os efeitos anti-inflamatórios dessas drogas. A segunda geração de anti-histamínicos difere da primeira geração devido a sua elevada especificidade e afinidade pelos receptores H1 periféricos e devido a seu menor efeito no sistema nervoso central, tendo como resultado menores efeitos sedativos. Embora a eficácia dos diferentes anti-histamínicos H1 (anti-H1) no tratamento de doentes alérgicos seja similar, mesmo quando se comparam anti-H1 de primeira e de segunda geração, eles são muito diferentes em termos de estrutura química, farmacologia e propriedades tóxicas. Consequentemente o conhecimento de suas características farmacocinéticas e farmacodinâmicas é importante para a melhor prática médica, especialmente em gestantes, crianças, idosos e doentes com comorbidades.
Palavras-chave: Antagonistas da histamina H1 não sedativos; Antagonistas dos receptores H1 de histamina; Histamina; Liberação de histamina; Receptores de histamina; Receptores de histamina H1

Approved by the Editorial Board and accepted for publication on February 12th, 2009.
* Work conducted at the Division of Dermatology, Clinical Hospital, University of Sao Paulo Medical School (HC-FMUSP), and Discipline of Dermatology, Faculty of Medicine of ABC - Sao Paulo (SP), Brazil.
Conflict of Interest / *Conflito de interesse*: Paulo Ricardo Criado: offered medical consulting services to the following laboratories: Libbs, Mantecorp, Schering-Plough and Theraskin. Roberta Fachini Jardim Criado: offered medical consulting services to the following laboratories: Mantecorp and Schering-Plough.
Financial funding: None / *Suporte financeiro: Nenhum*

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## INTRODUCTION

Over the last decade, important advances occurred in our knowledge about the mechanisms through which $H_1$ antihistamines produce their desirable effects and adverse reactions. This review presents the most recent advances in the three areas of the biology of antihistamines (molecular mechanisms through which antihistamines interact with histamine receptors; the possible anti-inflammatory action of these drugs, and the mechanisms, both genetic and pharmacological, through which their adverse effects occur), in addition to their indications for dermatologic conditions in children and adults.

### Histamine and its receptors

Histamine is synthesized and released by different human cells, especially basophils, mast cells, platelets, histaminergic neurons, lymphocytes, and enterochromaffin cells. It is stored in vesicles or granules released on stimulation. [1,2] Histamine (2-[4-emidazolyl]ethylamine) was discovered in 1910 by Dale and Laidlaw and identified as a mediator of anaphylactic reactions in 1932. [2] Histamine belongs to the biogenic amines and is synthesized by the pyridoxal phosphate (vitamin B6)-containing L-histidine decarboxylase (HDC) from the amino acid histidine.[2] Histamine is a potent mediator of numerous physiologic reactions.

Histamine exerts its effects on target cells in various tissues by binding to its four receptors: histamine receptor $(HR)_1$, $HR_2$, $HR_3$, and $HR_4$. [1] Table 1 summarizes the particularities of each one of these receptor types. These receptors belong to the G protein-coupled receptors family (GPCRs). [1] $H_1$ receptor ($HR_1$) is codified in the human chromosome 3 and is responsible for many symptoms of allergic diseases, such as pruritus, rhinorrhea, bronchospasm, and contraction of the intestinal smooth muscle. [3] Activation of $HR_1$ stimulates the signaling pathways of inositol phospholipid culminating in the formation of inositol 1,4,5-triphosphate (InsP3) and diacylglycerol (DAG), leading to an increase in intracellular calcium. [4] Moreover, when $HR_1$ is stimulated, it can activate other intracellular signaling pathways, such as phospholipase D and phospholipase A. [4] Recently, it was shown that stimulation of $HR_1$ can activate the nuclear transcription factor KB ($NF_kB$). Both are involved in the development of allergic diseases. [4]

Historically, the potency of antihistamines was verified through standard pharmacological trials, particularly from guinea pig ileum or tracheal smooth muscle contraction.[4] In these tissues, the drugs cause a parallel displacement in the histamine concentration/response.[4] This behavior is consistent with their classification as competitive antagonists for histamine receptor and led to their classification as $H_1$ receptor antagonists. [4]

Knowledge of molecular biology advanced dramatically over the last few years, especially of the

**CHART 1:** Different histamine receptors

| Histamine receptor | Cell and tissue expression | Activated intracellular signals | G Proteins |
|---|---|---|---|
| HR1 | Nerve cells, airway and vascular smooth muscles, endothelial cells, hepatocytes, epithelial cells, neutrophils, eosinophils, monocytes, DC, T and B cells. | Main signaling: enhanced Ca2+ Others: PhLC, PhLD, cGMP, PhLA, NFκ B | $G_{q/11}$ |
| HR2 | Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes DC, T and B cells. | Main signaling: enhanced AMPc Others: Adenylate cyclase, c-Fos, c-Jun, PKC, p70S6K | $G_{\pm S}$ |
| HR3 | Histaminergic neurons, eosinophils, DC, monocytes low expression in peripheral tissues. It inhibits histamine release and synthesis. | Main signaling: inhibition of cAMP Others: enhanced Ca2+, MAP kinase. | $G_{i/o}$ |
| HR4 | high expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DC, T cells, basophils, mast cells, low expression in nerve cells, hepatocytes peripheral tissues, spleen, thymus, lung, small intestine, colon and heart. It stimulates chemotaxis of eosinophils and mast cells. | Enhanced Ca2+, inhibition of cAMP | $G_{i/o}$ |

Eos, eosinophils; B cells, B lymphocytes; T cells, T lymphocytes; PKC, protein kinase C; cAMP, cyclic adenosine monophosphate; PhLC, phospholipase C; PhLD, phospholipase D; PhLA, phospholipase A; NF_B, nuclear transcription factor Kappa
Adapted source: Jutel M, et al. [1]

GPCRs expression in recombinant cell systems. This has changed our understanding about the way that antihistamines interact with GPCRs to exert their effects. Classical models of GPCRs need histamine receptors to be occupied by antagonist agents, which initiate the activation of signal transduction pathways. [4] However, it has been recently shown that GPCRs may show spontaneous activation, which does not depend upon the occupation of the receptor by an antagonist. [4] This is denominated constitutional (physiological) activity of the receptor, which has led to a reclassification of the drugs that act on GPRCs. [5] (Ligand) drugs traditionally considered antagonists, are now called inverse agonists, that is, substances capable of reducing the constitutional activity of GPCRs, or neutral antagonists, when ligands do not alter the basal activity of these receptors (GPCRs), but interfere with the binding of their agonists. [4] Since antihistamines can theoretically be both inverse agonists and neutral antagonists, it is not yet clear whether the term "$H_1$ receptor antagonist" is accurate. [4] Thus, the adoption of the term "$H_1$ antihistamines" has been suggested. [4]

The observation that the constitutional activity of GPCRs is often associated with mutant GPCRs has strengthened the interest in this phenomenon as being the mechanism for several genetic diseases. [4]

The functional model of GPCRs is constituted by a dynamic equilibrium between its inactive (R) and active (R*) conformations (Figure 1). Based on this model, the spontaneous isomerization of HR, independently of the agonist (histamine), from the inactive state (R) to the active (R*), shifts the equilibrium towards the state of constitutional activity of the GPCRs.[4] This isomerization involves conformational alterations of the receptors, which can be spontaneous or induced by mutations that alter the intramolecular structure of GPCRs. [4] Agonists preferably bind to histamine receptors in their active state to increase their stability and force an equilibrium shift to the active state. The degree of the shift will depend on whether it is a full or partial agonist (Figure 2). Conversely, an inverse agonist preferably binds to the inactive state of the histamine receptor and moves the equilibrium in the opposite direction, that is, in the direction of the inactive state (R). The degree of this equilibrium shift will depend on the nature of the inverse agonist. [4] The neutral agonist does not differentiate between the active and inactive receptor state. Consequently, it binds to both the active and inactive states and does not shift the equilibrium between the two states; however, it interferes with the subsequent binding, both of agonists and inverse agonists. [4]

Constitutional activity has already been shown

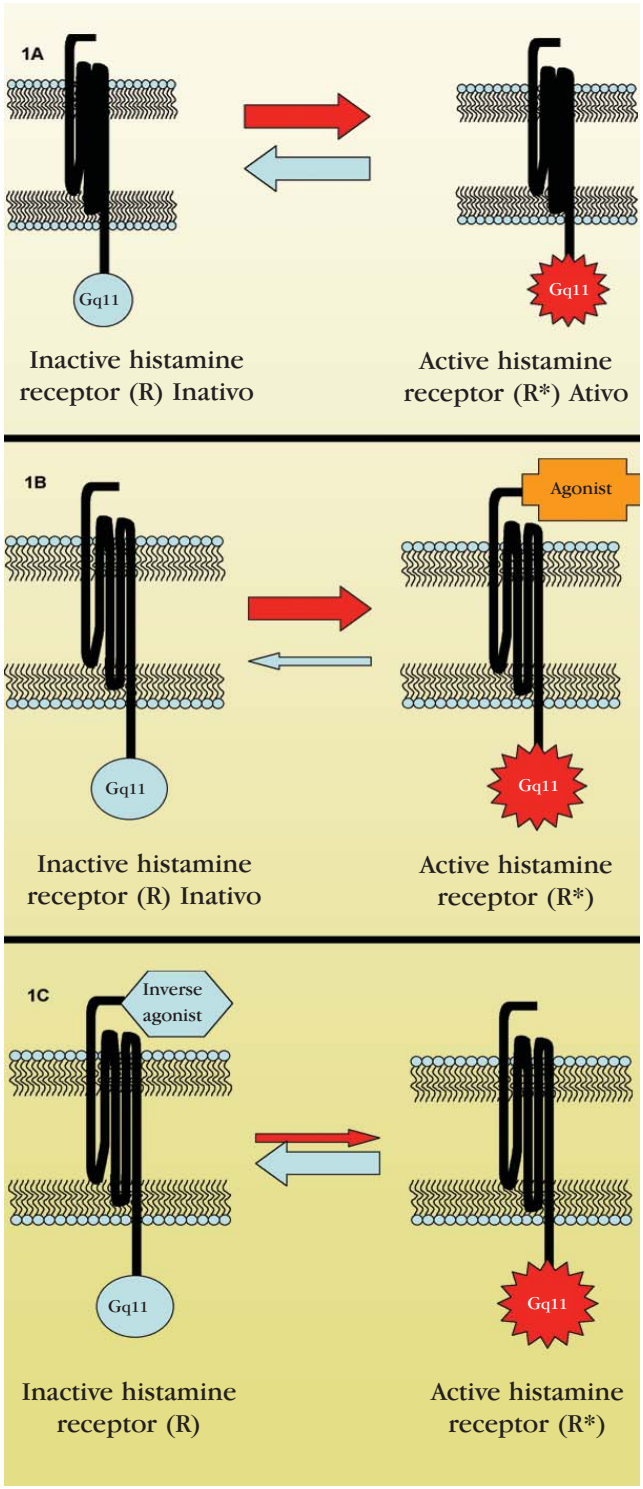


**Figure 1:** Functional model of histamine receptors. Simplified two-state model of histamine H1 receptor. A. at rest, the inactive state (R) isomerizes with the active state (R*) and vice versa to set up an equilibrium between the two states; B. an agonist, which has a preferential affinity for the active (R*) state, stabilizes the receptor in this conformation and, consequently, causes a shift in the equilibrium towards the active (R*) state. C. an inverse agonist, which has a preferential affinity for the inactive (R) state, stabilizes the receptor in this conformation and, consequently, causes a shift in the equilibrium towards the inactive (R) state

Adapted source: Leurs R, et al. [5]

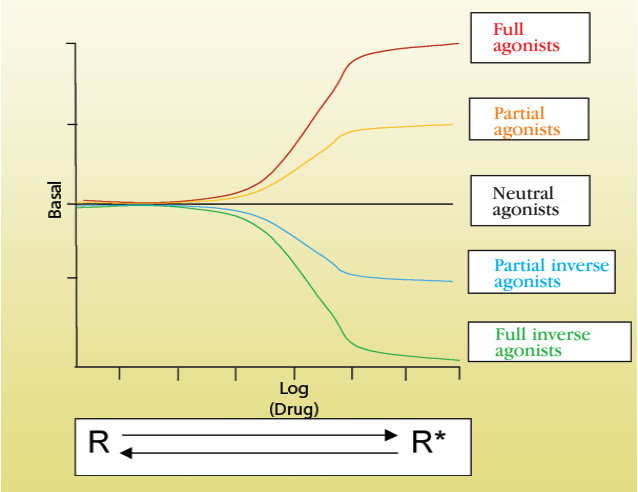


**Figure 2:** Equilibrium of histamine receptors upon exposure to neutral, partial, full, and inverse agonists. On the basis of the two-state model, ligands may now be reclassified as agonists, both full and partial, which stabilize the active state (R*) and increase receptor signaling. Inverse agonists, full and partial, stabilize the inactive state (R) and decrease basal receptor signaling. Neutral antagonists, which have equal affinity for both R and R* and, therefore, do not affect the equilibrium between the two states, reduce the ability of both agonists and inverse agonists to bind to the receptor

Fonte adaptada: Leurs R, et al.[3]

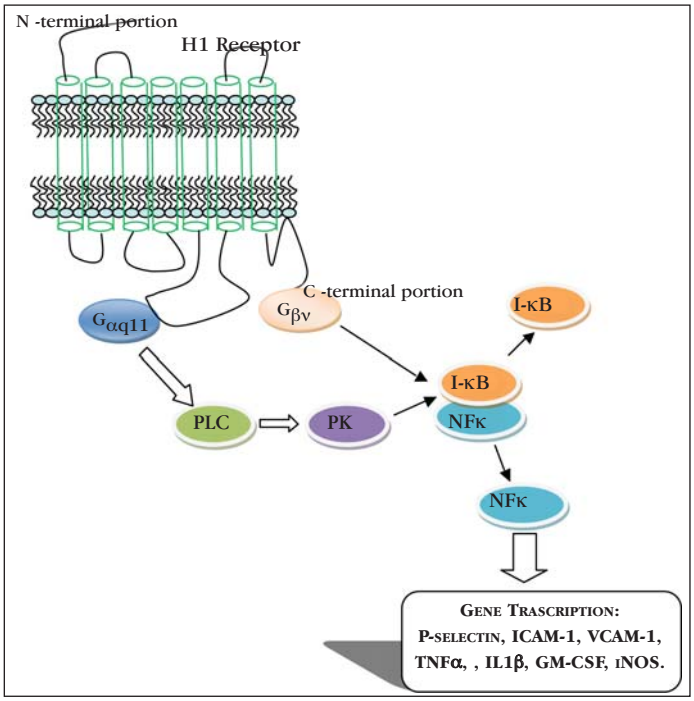


**Figure 3:** H1 receptors and their action on the gene transcription of inflammatory mediators. When histamine binds to H1 receptors (HR1), a stimulus and conformational change of this receptor occurs, which activate two pathways: (i) phospholipase C (PLC), activating the protein kinase C (PKC) and separating the dimer formed by I-κB and NFκB. This results in the release of NFκB, which enters the cell nucleus and stimulates the activation of the codifying genes of inflammatory mediators; (ii) at the same time, the pathway of Gβγ protein separates the dimer composed by I-κB and NFκB

Adapted source: Leurs R, et al. [3]

for the four types of histamine receptors. [6,7,8] Therefore, identification of the constitutional activity of the $H_1$ receptor has suggested that the inverse agonist could be the action mechanism of the then-called $H_1$ antagonists and now called $H_1$ antihistamines.

In addition, the constitutional activity of $H_1$ receptors is not restricted to the activation of phospholipase C (PLC), but it also activates the entire genetic transcription mediated by the kappa B nuclear factor (NFκB) (Figure 3).[4] The constitutional activity of the $H_1$ receptor mediating NFκB activation was inhibited by all the antihistamines tested by Bakker et al. [6], including cetirizine, ebastine, epinastine, fexofenadine, loratadine, and mezolastine. This indicates that all these agents act as inverse agonists.

### *Anti-inflammatory properties of $H_1$ antihistamines*

Since 1953, when Arunlakshana and Schild [9] showed that H1 antihistamines had the ability to inhibit the release of histamine from mast cells, several *in vitro* and *in vivo* studies have been conducted to determine whether these drugs have properties, other than the inhibition of histamine effects, that could contribute to the clinical efficacy of allergic diseases control. It has been postulated that some of the anti-inflammatory effects of H1 antihistamines follow their interaction with HRs, whereas others are independent of these receptors. [4]

In reality, these anti-inflammatory effects are questioned when studied *in vivo*. In 1996, Perzanowska et al.[9] administered orally two H1 antihistamines – cetirizine and loratadine – both in the dose of 10 mg/day, four hours before the induction of histamine release through codeine intradermal injections of 3 mg/L and 10 mg/L. Results showed a clear reduction of the allergic response in the development of the erythema and dermal edema. This shows that both drugs were absorbed and presented bioactivity. However, through dermal microdialysis technique, used to recover the histamine released in the extracellular fluid, it was observed that neither drug reduced histamine release. Therefore, it seems unlikely that inhibition of histamine release from mast cells contributes to therapeutic effects in the treatment of allergic and inflammatory reactions. Since the concentration of these drugs needed to avoid the release of histamines from mast cells and basophils *in vitro* is from 1 to 10 $\mu$M, and thus higher than those obtained *in vivo*, the anti-inflammatory effect appears irrelevant from a clinical standpoint. [4]

A possible mechanism of action of the inhibition effect of H1 antihistamines on the accumulation of inflammatory cells and their activation on tissues is

its capacity to suppress NFκB activation, as described by Bakker et al. [6] The NFκB is an omnipresent transcription factor which binds to regions that promote many genes that regulate the production of pro-inflammatory cytokines and adhesion molecules (Figure 3). The NFκB can be activated by histamine and TNF α.[6,10] Low concentrations of cetirizine and azelastine suppressed the expression of NFkB in a parallel manner with the synthesis of cytokines, IL1β, IL6, IL8, TNFα and GM-CSF.[11-13] In various clinical studies, cetirizine, azelastine, loratadine, and levocarbastine reduced ICAM-1 expression. [4,11-14]

If these important anti-inflammatory effects are secondary to their interaction with HRs, they will occur for all H1antihistamines clinically used. Nevertheless, the intensity of these effects will depend upon their antihistaminic potency and their dose. [4]

**Pharmacology of antihistamines**

Although the efficacy of the different $H_1$ antihistamines in the treatment of allergic patients is similar, even when first and second generation antihistamines are compared, they are very different in terms of their chemical structure, pharmacology and toxic potential. [15] Therefore, knowledge about their pharmacokinetic and pharmacodynamic characteristics becomes relevant to the clinical use of these drugs, especially in very young and old individuals, pregnant women and patients with co-morbidities.

***Absorption***

Most $H_1$ antihistamines have good absorption when administered orally, since most of them reach effective plasma concentration within three hours after administration (Chart 2). [16] The good liposolubility of these molecules allows them to easily cross cellular membranes, which facilitates their bioavailability. [16]

In some cases, the concomitant administration of these drugs with the ingestion of particular food items may alter their plasmatic concentration. [16] This is explained by the presence of active transporting mechanisms of cellular membranes. The most well-known mechanisms are P glycoprotein (gP) and organic anions transporting polypeptides (OATP). [16] These glycoproteins and polypeptides are found in the cellular membrane and serve as active transporting systems for other molecules, for which they show affinity. In some cases, these systems act as important elements in the absorption and/or clearance of a few drugs. In other circumstances, they promote tissue detoxification, depending on whether these transporting systems are localized in the cellular membranes of the intestinal epithelium (drug absorption) or in the central nervous system (blood-brain barrier, BHL) or kidneys (excretion), where they detoxify from drugs. [16]

A few antihistamines behave as substrates of these transporting systems, such as fexofenadine. [17] However, other drugs, such as desloratadine, do not have their intestinal absorption influenced by transporting systems. [18] Variations in the bioavailability of a few antihistamines have been documented. When a few antihistamines, such as fexofenadine, are ingested with food that serves as a glycoprotein substrate, like grape or orange juice, or with drugs that also have this property, such as verapamil, cimetidine, and probenecid, variations in their bioavailability have been documented. [19]

***Metabolism and Excretion***

Most $H_1$ antihistamines are metabolized and detoxified in the liver by a group of enzymes that belong to the cytochrome p450 system (CYP). Only acrivastine, cetirizine, levocetirizine, fexofenadine, and desloratadine [20] prevent this metabolic passage to a relevant extent, which makes them more predictable regarding their desirable effects and adverse reactions. [16] Cetirizine and levocetirizine are eliminated in urine, mainly in their unaltered form, whereas fexofenadine is eliminated in feces, after biliary excretion, without metabolic alterations. [15] Other $H_1$ antihistamines are transformed in the liver into active or inactive metabolites, whose plasmatic concentration depends on the CYP system activity. This activity is, on its turn, genetically determined; thus, some individuals have a high intrinsic activity of these pathways, while others show a reduced activity of this enzymatic system, namely the CYP3A4 or CYP2D6. [15] In addition, the CYP system can be altered in special metabolic conditions, such as infancy, advanced age, hepatic diseases or by the direct action of other drugs which accelerate or delay the action of these enzymes in the metabolism of $H_1$ antihistamines.

Drug interactions decrease the plasmatic concentration of $H_1$ antihistamines and, consequently, reduce their clinical efficacy, such as when CYP3A4 inductors are administered; for example, benzodiazepines with $H_1$ antihistamines. [21] Conversely, we can increase the concentration of $H_1$ antihistamines and their bioavailability, thus intensifying their adverse reactions, such as when drugs that competitively inhibit their metabolism by CYP are administered; for instance, with the concomitant use of macrolides, antifungal drugs, and calcium channel antagonists. [22] In such cases, the safety margins of $H_1$ antihistamines are minimal, with greater likelihood of adverse effects since their plasma levels are unpredictable. [16]

P glycoprotein (gP) (Figure 4) consists of a natural system of detoxification expressed in normal human tissues, which have secretion or barrier

**CHART 2:** Absorption, doses, and metabolism of H1 antihistamines

| Generation | Drug | Children dose (day) | Adult dose (day) | Max T* | Duration of action (hours) | Hepatic metabolism | Drug interactions | Dose adjustment |
|---|---|---|---|---|---|---|---|---|
| 1st | Chlorpheniramine (Dex♦) | 0.15 mg/kg/day | 2-8mg/day,+ 3 doses | 2.8±0.8 | 24 | Yes | Possible | U |
| | Clemastine♦ | 0.5 ml/kg/day | 2mg | U | U | Yes | Possible | U |
| | Cyproheptadine♦ | 0.125mg/kg/day | 2-8mg<br>50 to 400mg | U | U | Yes | Possible | HI |
| | Diphenhydramine | 5mg/Kg + 3 to 4x/day | | 1.7±1.0 | 12 | Yes | Possible | HI |
| | Doxepine♦ | Not used | 10-100mg | 2 | U | Yes | Possible | HI |
| | Hydroxyzine♦ | 1-2mg/kg/day | 10-200mg | 2.1±0.4 | 24 | Yes | Possible | HI |
| 2nd | Acrivastine | U | unavailable | 1.4±0.4 | 8 | <50% | Unlikely | U |
| | Ketotifen♦ | 0.05mg/kg/day | 1-2mg | 3.6±1.6 | 12 | Yes (?) | U | HI and RI |
| | Cetirizine♦ | 2-6 yrs: 2.5 mg, **2x/ day**;<br>6-12 yrs: 5mg; **2x / day** | 10mg | 1.0±0.5 | ≥24 | <40% | Unlikely | HI and RI |
| | Loratadine♦/ Decarboetoxilo-ratadine | 2-6 yrs,2.5 mg,6-12 yrs,5mg;**1x /day** | 10mg | 1.2±0.3<br>1.5±0.7 | 24 | Yes | Very likely | HI and RI |
| | Ebastine♦/ Carebastine | 2-6 yrs,2.5 mg,6-12 yrs,5mg; 1x / day | 10mg | 2.6±5.7 | ≥24 | Yes | Possible | HI and RI |
| | Fexofenadine♦ | 6 mos-2 yrs: 2.5ml (15mg) 2x/day;<br>2-11yrs: 5ml (30mg) 2x/day;<br>>12 yrs: 60 mg 2x/day | 120mg<br>180mg | 2.6 | 24 | <8%<br>Yes | Yes (P glycoprotein) | RI |
| | Mizolastine | U | 10mg | 1.5 | 24 | Yes | Possible | HI |
| | Levocetirizina♦ | >6yrs (5mg/day) | 5mg | 0.8±0.5 | ≥24 | <15% | Unlikely | IH e IR |
| | Desloratadine♦ | 6mos-1yr: 1mg/day;<br>1-6 yrs,1.25 mg/day;<br>6-12 yrs: 2.5mg /**day** | 5mg | 1-3 | ≥24 | Yes | Unlikely | HI and RI |
| | Rupatadine♦ | Não tem | 10mg | 0.75 | 13 | Yes | Improvável | HI and RI |

♦ Available in the Brazilian market; U, unavailable information; Max T*, time between oral ingestion and peak plasmatic concentration; HI, hepatic insufficiency; RI, renal insufficiency

functions. [23] This system is found in the small and large intestines, biliary canaliculi, proximal renal tubules, endothelial cells of the central nervous system (CNS), placenta, adrenal glands and testicles. [23-25]P glycoprotein acts as an extraction pump and is considered important in the distribution and excretion of various drugs and their interaction. [23-25]

The plasmatic concentration of $H_1$ antihistamines may be altered in the presence of gP inhibitors, such as ketoconazole, cyclosporine and verapamil or itraconazole; of substrates and gP inhibitors, such as erythromycin, azythromycin, verapamil or itraconazole; or of gP inducers, such as verapamil or rifampin, since most of them, if not all, are gP substrates to a higher or lower degree. [23]

It is relevant to stress that many drugs or substances that act as substrates or modulators of gP activity have the same functions in other metabolic systems, such as CYP3A4 or in the family of organic anion-transporting polypeptides (OATP). [23] This may make interactions among different drugs possible. [23]

Members of the organic anion transporting polypeptides family (OATP) identified in humans include: (i) OATP-A, expressed in endothelial cells; (ii) OATP-B, vastly distributed in various tissues, such as intestines and liver, and (iii) OATP-8, expressed only in the liver. [23] Their function is to participate in the distribution and excretion of drugs and other substances in the same way as P glycoprotein, although in the opposite direction. [23] The function of the OATP family in the pharmacokinetics of $H_1$ antihistamines has been reviewed particularly in relation to fexofenadine and desloratadine. [23] In this context, fexofenadine is a substrate of OATP-A, whereas desloratadine is not. [23]

In the same way that $H_1$ antihistamines can interact with other drugs in a metabolic level, this can also occur with elements present in food. [23]

It is known that the concomitant ingestion of grapefruit juice raises the plasmatic levels of certain drugs, such cyclosporine, calcium antagonists, and benzodiazepines, among others. [23] This effect has been attributed to the capacity of grapefruit to inhibit CYP3A4 at the intestinal level. [23] Intestinal CYP3A4 contributes as a first step to the metabolism of certain substances, such as $H_1$ antihistamines. [23] Therefore, it is expected that grapefruit juice increase the bioavailability of $H_1$ antihistamines through their interaction in the intestines. [23] Moreover, grapefruit juice is also a

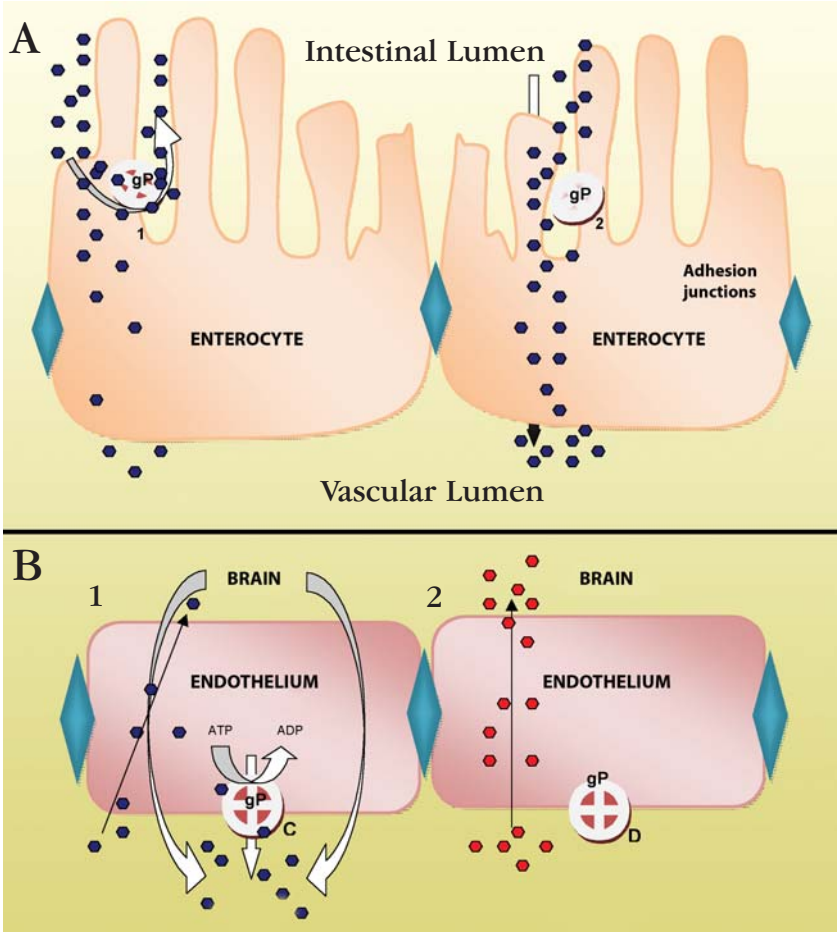


**FIGURE 4:** P glycoprotein in the intestines and blood-brain barrier.
**A.** 1. The substrates of P glycoprotein (gP) are absorbed in the intestinal lumen and move in the direction of the enterocyte to be sent to the blood circulation. Substances that are a substrate of gP are picked up from the cytoplasm of the enterocyte and sent retrogressively to the intestinal lumen by this active transporting system. 2. Substances that are not substrates of gP (or when gP-inhibiting drugs are co-administered) are absorbed in the intestinal lumen and transferred to the blood circulation. **B.** 1. Several substances such as second-generation H1 antihistamines reach the CNS through the cerebral circulation and are passively transferred to the endothelium in the blood-brain barrier. However, since they are substrates of gP, they are actively transported in a retrograde way to the cerebral circulation and minimum amounts bind to histamine receptors in the brain. However, when drugs that are not substrates of gP enter the cerebral circulation, such as first-generation H1 antihistamines, they passively spread through the blood-brain barrier and are not removed from the CNS, binding profusely to H1 receptors in the brain and causing adverse effects

gP inducer, so drugs that are a substrate of the gP transporting system my have their bioavailability reduced due to those interactions. [23]

The components of grapefruit juice that appear to be involved in such interactions are flavonoids and furanocoumarins. [23] The flavanoid naringin, specific to grapefruit juice, inhibits CYP3A4, mediated by the active metabolite naringenin. [23] The furanocoumarin bergamottin is also a potent inhibitor of CYP3A4. [23] Thus, it seems that inhibition of the metabolism of certain drugs at the intestines may be the result of the effects of flavonoids and furanocoumarins on CYP3A4. [23]

Most $H_1$ antihistamines are excreted by the kidneys after metabolization to a greater or lower extent. [15]Biliary excretion is possible and is more intensely performed by fexofenadine and rupatadine – the first without metabolization and the second after extensive metabolization. [15] Dose adjustment may be necessary when renal or hepatic functions are reduced or in elderly patients or those with renal or hepatic insufficiency.[15]

### Classical or first-generation $H_1$ antihistamines

Classical antihistamines are lipophilic drugs classified into different groups according to their chemical structure (Chart 3). [26] All of them are metabolized by CYP in the liver and do not serve as gP substrates. [23,27,28] Although not all metabolic pathways are completely known, most classical $H_1$ antihistamines are metabolized by CYP2D6, and some of them by CYP3A4. [23,27] Studies based on the use of diphenhydramine, as an example of a first-generation $H_1$ antihistamine, have shown that these drugs are not only CYP2D6 substrates, but also inhibit this pathway of cytochrome p450. [23] This should be considered when other drugs that use this metabolic pathway are administered concomitantly, such as metoprolol, tricyclic antidepressants and tramadol. [23] Moreover, classical $H_1$ antihistamines have several adverse effects due to their actions in muscarinic (anticholinergic effect), serotoninergic, and adrenergic receptors, among others, as shown in Figure 5. [16]

First generation $H_1$ antihistamines are rapidly absorbed and metabolized, which means that they should be administered three or four times a day. [26] Due to their lipophilic molecular structure, they cross the blood-brain barrier, bind easily to the cerebral $H_1$ receptors (Figure 4), and thereby create their main

adverse effect: sedation.[26] In addition, they do not behave as P glycoprotein substrate in the endothelium of the blood-brain vessels. The main differences between first and second generation $H_1$ antihistamines are listed in chart 4.

**Second-generation $H_1$ antihistamines**

Second-generation $H_1$ antihistamines are substances developed over the last 25 years. Some are derived from first-generation $H_1$ antihistamines, but they offer greater advantages in relation to first generation compounds because of their reduced anticholinergic or sedative effects. [23] However, they also have adverse effects and some of them interact with other drugs and substances. [23]

Metabolic interactions of second-generation $H_1$ antihistamines, such as terfenadine, astemizol, loratadine, desloratadine, ebastine, fexofenadine, cetirizine, levocetirizine, mizolastine, epinastine, and rupatadine have been intensively studied, since the first reports of severe cardiac arrhythmia associated with the use of terfenadine. [23,29] In general, we can state that second-generation $H_1$ antihistamines act as a gP substrates. [23] Due to this fact, they have less sedative effects than first-generation $H_1$ antihistamines, since they are removed from the CNS by gP (Figure 4). [23] Nonetheless, a few second-generation $H_1$ antihistamines undergo an important initial metabolization in the liver or intestine, mediated by CYP. [23]

The metabolism of $H_1$ antihistamines via CYP3A4 became relevant due to observations of drug interactions between terfenadine, erythromycin, and ketoconazole.[23] Later, other CYP3A4 substrates and/or inhibitors, such as fluoxetine, troleandomycin and zileuton, among other drugs, were investigated in relation to their interaction with terfenadine, which has its plasmatic levels increased when co-administered with these drugs. [23]

*Fexofenadine* is not metabolized via CYP and 95% of the molecules are recovered in urine and feces. [23]Therefore, it does not interact with CYP3A4 inhibitors or other isoenzymes. Evidence indicates that fexofenadine is safe and well-tolerated since its cardiovascular safety has been convincingly demonstrated even at high dosages. [23] When fexofenadine is co-administered with a gP inhibitor, its levels increase by threefold in the plasma. [23] Fexofenadine is a potent gP substrate; as such, much of its bioavailability and elimination depends on this transporting system. [7] Drugs or substances capable of inducing gP, like rifampicin, lower the concentration of fexofenadine in the blood, which reduces the efficacy of the drug. [23] However, when fexofenadine is co-administered with probenecid (an OATP inhibitor), its blood concentration increases significantly with reduced renal excretion. [23] It has been shown that grapefruit juice interacts with fexofenadine at the gP level determining a reduction in its serum levels. This has also been observed with orange and apple juice. [23] Dose adjustment is needed in case of renal dysfunction. [15]

*Loratadine* is also first metabolized in the liver, since it is almost completely metabolized by CYP, forming a variety of metabolites. [23] One of its metabolites is desloratadine, which after metabolization originates the active molecule decarboetoxyloratadine. Its formation is mediated both by CYP3A4 and CYP2D6.[30] Based on this profile, loratadine may interact with other drugs metabolized by CYP. [23] Loratadine may act both as a substrate and a potent gP system inhibitor, but in a smaller scale than

**Chart 3:** Chemical classification of H1 antihistamines

| Alkylamines | Ethanolamines | Ethylenediamines | Phenothiazines | Piperazines | Piperidines |
|---|---|---|---|---|---|
| Bromopheniramine[1] | Carbinoxamine[1] | Antazoline[1] | Promethazine[1] | Buclizine[1] | Azatadine[1] |
| Chlorpheniramine[1] | Clemastine[1] | Pyrilamine[1] | Mequitazine[1] | Cyclizine[1] | Cyproheptadine[1] |
| Dexchlorpheniramine[1] | Dimenhydrinate[1] | Tripelenamine[1] | Trimepazine[1] | Meclizine[1] | Ketotifen[1] |
| Pheniramine[1] | Diphenhydramine[1] | | | Oxatomide[1] | Loratadine[2] |
| Dimethindene[1] | Doxylamine[1] | | | Hydroxyzine[1] | Desloratadine[2] |
| Triprolidine[1] | Phenyltoxamine[1] | | | Cetirizine[2] | Bilastine[2] |
| Acrivastine[1] | | | | Levocetirizine[2] | Ebastine[2] |
| | | | | | Terfenadine[2] |
| | | | | | Fexofenadine[2] |
| | | | | | Levocabastine[2] |
| | | | | | Mizolastine[2] |
| | | | | | Rupatadine[2] |

[1] classical or first-generation H1 antihistamines; [2] second-generation H1 antihistamines
Adapted source: de Benedictis FM, et al.[26]

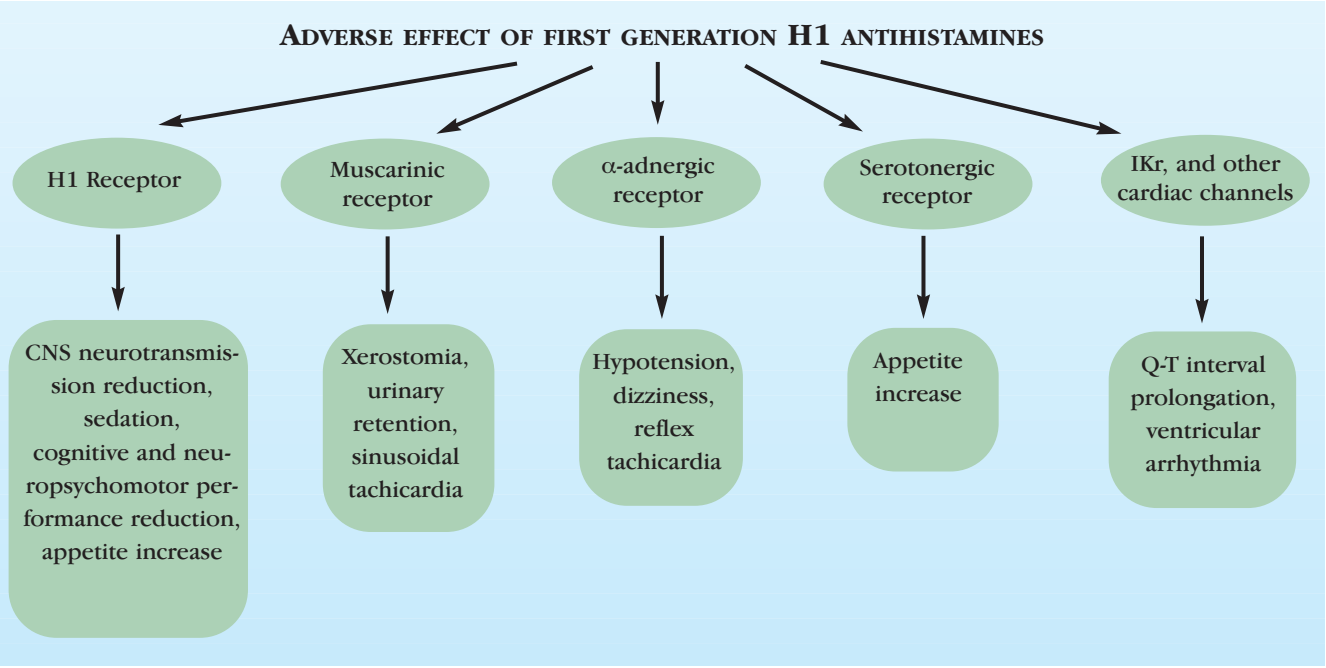


**FIGURE 5:** Symptoms and signs of the adverse effects of first-generation H1 antihistamines

verapamil and cyclosporine. Thus, pharmacologic interactions may occur. [23] Dose adjustment is necessary in cases of renal or hepatic insufficiency. [15] About 46% of the maternal therapeutic dosage of loratadine is passed on to breast milk. [15]

Adverse electrocardiographic effects were not observed, although desloratadine, when co-administered with CYP inhibitors (especially CYP3A4, erythromycin, and ketoconazole), has had a slight increase in its plasmatic concentration. [31] Grapefruit juice does not appear to interact with desloratadine. [23] In the pediatric population, pharmacokinetic studies with desloratadine have been conducted with preschoolers and school-aged children. [26] Desloratadine dosages for children aged 2 to 5 years are 1.25 mg (2.5 ml) and for children aged 6 to 11 years, 2.5 mg (5ml). [26] When children aged ≥6 months and -≤ 2 years were studied with doses of 1mg for children ≤ 6 months ≤1 year and of 1.25 mg for children ≥1 year and ≤2 years, the efficacy and

**CHART 4:** Differences between first and second-generation H1 antihistamines

| First-generation H1 antihistamines | Second-generation H1 antihistamines |
|---|---|
| Usually administered in three to four daily doses | Usually administered once or twice a day |
| Cross the blood-brain barrier (lipophilicity, low molecular weight, lack of recognition by the P-glycoprotein efflux pump | Do not cross the blood-brain barrier (lipophobicity, high molecular weight, recognition by the P-glycoprotein efflux pump) |
| Potentially cause side-effects (sedation/ hyperactivity/insomnia/convulsions) | Do not cause relevant side-effects (sedation/fatigue/hyperactivity/convulsions), in the absence of drug interactions |
| Case reports of toxicity are regularly published | No reports of serious toxicity |
| No randomized, double-blind, placebo-controlled trials in children | Some randomized, double-blind, placebo-controlled studies in children |
| Lethal dose identified for infants/young children | Do not cause fatality in overdose |

Adapted source: de Benedictis FM, et al.[26]

tolerability of the drug were adequate. [26]

*Ebastine* is chemically associated with terfenadine and it is completely transformed via CYP3A4 into metabolites, among which carebastine is the active one. [34] When ebastine is co-administered with CYP3A4 inhibitors, its serum levels increase. [23] This may result in changes in electrocardiographic activity. Therefore, ebastine has arrhythmogenic potential due to drug interactions. [35,36] Dose adjustment is necessary in case of hepatic insufficiency. [15]

*Mizolastine* undergoes important hepatic metabolization via glucoronidation, with little CYP participation. [37] As a result, the drug is mainly eliminated as conjugates without transformation into active metabolites. [23] Serum levels of mizolastine increase when it is co-administered with ketoconazole or erythromycin, although without relevance from an electric cardiac activity standpoint. [23] Regarding the gP system, information about mizolastine is scarce and limited to an increase in the levels of digoxin (a gP substrate), when co-administered. It appears that mizolastine behaves as a gP inhibitor. [23] There are no data about the need for dose adjustment in the presence of renal or hepatic disease. [15]

*Epinastine* does not undergo metabolization in the liver and, as a consequence, does not interact with CYP inhibitors or inducers. It also does not show adverse cardiac effects. [38,39]

*Cetirizine* is a carboxylic acid with a racemic mixture of R and S enantiomers, derived from hydroxyzine. [23] It is not metabolized in the liver and does not interact with CYP met inducers or inhibitors in the liver. [23] Changes in electrocardiography have not been observed when cetirizine is administered up to 6 times the recommended dose. [40] Cetirizine appears to be a substrate of gP; thus, drug interactions at this level are possible, but are not yet fully explained. [28] Dose adjustment is necessary with advanced age and renal or hepatic diseases. [15]

*Levocetirizine* is the active R-enantiomer of racemic cetirizine that obviously does not undergo hepatic metabolization, does not have adverse cardiac effects or drug interactions documented. [41] Levocetirizine is a weak gP substrate; hence, its interaction with other drugs is unlikely in this transporting system. [23] In studies with children from 6 to 12 years old with allergic rhinitis in which levocetirizine was administered for four weeks at a dosage of 5mg/day (adult dosage), the drug showed a minimum incidence of adverse effects, compared to those of placebo. [42,43]

Rupatadine is metabolized by CYP in the liver and interacts with other drugs metabolized by this system. However, adverse cardiac effects have not been reported. [44]

**Effects on the central nervous system**

First-generation $H_1$ antihistamines are lipophilic drugs with little affinity for gP, whereas second-generation $H_1$ antihistamines are lipophobic drugs with affinity for gP. The difference between these two groups of drugs based on their molecular weight (theory that smaller molecules cross the blood-brain barrier more easily) is becoming less relevant. [45] As an example, the molecular weight of desloratadine is 338.9 and is similar to that of hydroxyzine (molecular weight 347.9); however, the permanence time of these two drugs in the cerebral tissues is different. [45]

The criteria to classify the sedative effects of an $H_1$ antihistamine are based on three parameters that should be minimally evaluated: (i) subjective impact on somnolence (its presence); (ii) objective evaluation of changes in cognitive and psychomotor activities, and (iii) occupation of central $H_1$ receptors in studies based on positron emission tomography (PET). [45] Although the last two criteria are relevant, all three must be present for a drug to be classified as having sedative action. [46]

Tagawa et al. [47], in a placebo-controlled study, evaluated the effects of ebastine 10 mg and chlorpheniramine 2mg on the central nervous system. Cerebral $H_1$-receptor occupation was correlated with chlorpheniramine plasma levels and determined cognitive function deterioration. Nevertheless, this was not observed for ebastine (specifically for its active metabolite carebastine). In fact, cerebral $H_1$-receptor occupation by ebastine ($HR_1$) was about 10%, while chlorpheniramine 2mg exceeded 50%. In general, percentile cerebral $HR_1$ occupation by second-generation $H_1$ antihistamines varies between 10-30% (cetirizine), although fexofenadine appears not to occupy them. [48]

For an $H_1$ antihistamine not to be considered sedative, its $H_1$-receptor occupation in the CNS should not exceed 20% when administered at the maximum recommended dosage. Central adverse manifestations appear when around 50% of $H_1$ receptors are occupied. However, some authors believe that this happens with occupation of 60 to 70% of $HR_1$. [47,48]

Generally, after various tests (visual, oculomotor, visual and acoustic signal detection and identification, in addition to decision-making tests), second-generation $H_1$ antihistamines do not differ significantly from the placebo in relation to effects on the CNS when administered at a single dose or for 4 to 5 days. [45] Conversely, first-generation $H_1$ antihistamines showed alterations in the tests performed. [45,49] A tolerance phenomenon is known to occur with first-generation $H_1$ antihistamines when administered for 4 to 5 consecutive days, with a marked reduction of their

adverse effects on the CNS. [45]

It should be considered that most data obtained come from studies with healthy volunteers. [45] This makes it difficult to extrapolate these results to the rest of the population, since allergic individuals are influenced by the presence of inflammatory mediators in the physiopathogeny of these diseases. This may determine changes in capillary permeability, not only at peripheral level, but also in the blood-brain barrier, leading to more adverse effects on the CNS. [45]

**Adverse Cardiac Effects**

It is known that potassium channels blockage in the heart (Kv11.1 channels, codified by the human ether-a-go-go related gene) can extend the QT interval in the electrocardiogram, causing potentially severe and fatal arrhythmias. [50] Fexofenadine, administered at doses of 1400mg for a week to healthy volunteers, did not change the QT interval, even when co-administered with ketoconazole or erythromycin. [50]

Apparently, hydroxyzine does not induce ventricular arrhythmias, although changes in T waves have been reported when it is administered in high doses. [51] Its metabolite cetirizine does not block Kv11.1 channels, even in high concentration and under different circumstances. It is thus rarely associated with adverse cardiac effects.[50] Levocetirizine seems to behave in a similar way. [50]

Ebastine may interact with Kv11.1 channels, although adverse cardiac effects have not been reported. [50] In a study in which ebastine was administered at a total dose of 50 mg (5 times the recommended dosage), effects on the QT interval where not observed. [50] However, caution should be exercised with patients with a long QT interval who use drugs that affect CYP or who have hypocalcemia. [50] Apparently, carebastine does not block potassium channels in the heart. [50]

Loratadine exerts a few effects on Kv11.1 channels. [50] The concomitant use of loratadine with drugs that inhibit CYP3A4 increases its concentration, but often without extension of the QT interval, except when it is administered with nefazodone (antidepressant). [50] In general, loratadine apparently does not exert clinical effects on potassium channels. [50] Desloratadine, on its turn, appears not to block potassium channels. [50]

Mizolastine is structurally similar to astemizol and binds to cardiac potassium channels in higher concentrations than those obtained therapeutically, and it can induce blockage of these channels. [50] In healthy volunteers mizolastine did not change the QT interval, even in doses four times greater than routine. [50]

Rupatadine concentrations increase when the drug is co-administered with CYP inhibitors, although this does not appear to extend the QT interval, even when it is used with erythromycin and ketoconazole. [50]

Therefore, three possible questions should guide physicians before prescribing an $H_1$ antihistamine: (i) Does the patient have any form of cardiac disease? If yes, an $H_1$ antihistamine with little or no effect on Kv11.1 channels should be used; (ii) Is the patient using any of the following: macrolides, opiates, imidazolic compounds, antipsychotic, antimalarial or antimigraine drugs? If yes, then prescription of $H_1$ antihistamines should be cautious or avoided, because these drugs can extend cardiac repolarization;[50] (iii) Does the patient show any risk factor, such as special diet (grapefruit juice), hepatic disease, electrolytic disturbance, etc, and use of non-antiarrhythmic drugs with the potential of extending the QT interval? If yes, prescription of $H_1$ antihistamines should be preceded and followed by ECG and evaluation by a cardiologist. [50]

**$H_1$ antihistamines in atopic dermatitis**

Pruritus is the most frequent and less tolerable symptom in patients with atopic dermatitis (AD); its reduction or control can result in a significant improvement of these patients' quality of life. [26] Nevertheless, histamine is only one of the mediators of pruritus in atopic dermatitis, and the effect of $H_1$ antihistamines has been questioned. [26] Classical $H_1$ antihistamines have been prescribed at bedtime to treat pruritus due to its sedative effects. [26] Second-generation $H_1$ antihistamines have been ineffective to control pruritus in atopic dermatitis. [52]

**$H_1$ antihistamines in urticaria**

Second-generation $H_1$ antihistamines are the only drugs with class 1 evidence and A level of recommendation by evidence-based medicine (EBM) indicated for the treatment of chronic urticaria (CU), due to the existence of randomized prospective, double-blind, and placebo-controlled studies. [53] $H_1$ antihistamines are first line drugs indicated for the symptomatic treatment of CU. [26,52] Second-generation $H_1$ antihistamines offer moderate to good control in 44-91% of all types of urticaria and in 55% of CU patients. [54] All $H_1$ antihistamines are more effective in reducing pruritus than in decreasing the frequency, number or size of urticas. [55]

Some authors postulate that in young adults with associated disease, the dosage of second-generation $H_1$ antihistamines should be raised up to four times the recommended by the manufacturer, before replacing the treatment or adding another drug to the treatment of CU (off-label indications, non-approved by the Sanitary Vigilance Agency – ANVISA, in Brazil). [54] According to evidence-based medicine, this suggestion still corresponds to class 3 evidence and C level

of recommendation. [54] A recent study, in which cetirizine was administered to 22 CU patients disputed these recommendations, since no improvement was observed after two weeks of treatment with cetirizine 30 mg. [56] This result may be due to observation for a short time.

Classical $H_1$ antihistamines more widely used to treat CU belong to the ethanolamine group (diphenhydramine, clemastine), piperazine group (hydroxyzine, dexchlorpheniramine), and piperidine (cyproheptadine and ketotifen). [57] Ketotifen proved to be more effective than clemastine in a study with 305 patients with CU, although the incidence of adverse effects was similar (20 to 21% of the patients). [58]

A few randomized studies compared the effects of cetirizine in the treatment of CU both in relation to hydroxyzine[59] and loratadine.[57] They showed similar clinical efficacy, but with a greater safety profile for hydroxyzine.

In general, studies comparing the various second-generation $H_1$ antihistamines used in the treatment of CU have not showed significant differences in relation to control of the symptoms, patients' quality of life or safety profile. All of them are indicated as first line agents for the treatment of CU. [57] The different $H_1$ antihistamines available in the Brazilian market are listed in chart 5.

### $H_1$ antihistamines in special situations

*Gestation*

Data about the use of $H_1$ antihistamines in pregnancy are observational. $H_1$ antihistamines classified as **B** category by the FDA in the United States (risk not shown in animals, but without controlled human studies) are [60]: (i) **first-generation** $H_1$ antihistamines: chlorpheniramine, tripelennamine (available in Brazil only in association with systemic nasal decongestants not allowed in pregnancy); dexchlorpherinamine, dimenhydrinate, and cyproheptadine. These $H_1$ antihistamines must be the first choice in first trimester

**CHART 5:** Commercial names of H1 antihistamines available in the Brazilian market

Commercial names of H1 antihistamines administered orally, parenterally, nasally, and in the eye, used in the various medical specialties, are in the list. Antiemetic and orexigenic drugs are also included.

Antazolina (Albassol colírio®)
Azatadina (Cedrin®)
Bromofeniramina ou bronfeniramina (Bialerge®)
Buclizina (Apetibê suspensão®, Buclina®, Buclivit®, Carnabol®, Klizin®, Lanabol®, Lisinvitam®, Nutri-ped suspensão®, Nutrimaiz SM®, Postafen® - em geral usados para cinetose ou como orexígenos)
Carbinoxamina (Naldecon®)
Cetirizina (Zetalerg®, Cetrizin®, Zyrtec®, Zetir®, CetiHexal®, Zinetrin®)
Cetotifeno (Asdron®, Asmen®, Nemesil®, Zaditen®)
Clemastina (Agasten®)
Clorfeniramina (Resfenol®, associação paracetamol e efedrina)
Desloratadina (Desalex®)
Dexclorfeniramina (Polaramine®, Dexmine®, Desclofan®)
Difenidramina (Alergo filinal®, Difenidrin injetável® - 50 mg/ml)
Dimenidranato (Aziac®, Dimedril®, Dramavit®, Dramin®, Dramin B6 DL®)
Dimetindeno (Trimedal®)
Doxilamina (Bronco-ped®, Revenil®)
Ebastina (Ebastel®)
Epinastina (Talerc®)
Feniramina (Claril®)
Fexofenadina (Allegra®, Fexodane®)
Hidroxizina (Hixizine®, Prurizin®)
Levocetirizina (Zyxem®)
Loratadina (Claritin®, Loranil®, Loralerg®, Clarilerg®, Clistin®, Loremix®, Lorasc®)
Meclizina (Meclin®)
Mequitazina (Primasone®)
Pirilamina (Prenefrin nasal®, Alersan®)
Prometazina (Fenergan®, Pamergan®, Lisador®)
Rupatadina (Rupafin®)
Tripelenamina (Alergitrat gel®)
Tripolidina (Actifedrin®)

Data from the website: http://www.bulas.med.br/, accessed on 31 Jan. 2009

pregnancies due to the vast experience with its use and avoided in the third trimester due to the risk of neonatal seizures; (ii) **second-generation** $H_1$ antihistamines: loratadine and cetirizine.

The following are classified as **C** category drug (proved risk for animals or absence of studies with animals or humans) by the FDA: (i) **first-generation** $H_1$ antihistamines: brompheniramine, diphenhydramine, hydroxyzine, and clemastine; (ii) **second-generation** $H_1$ antihistamines: fexofenadine and ebastine.

*Lactation*

Classical antihistamines should be avoided during lactation, especially in the first months of the child's life due to the risk of irritability, sedation, and reduction of the mother's milk supply. [60] Manufacturers of the $H_1$ antihistamines cetirizine, cyproheptadine, hydroxyzine, loratadine, and mizolastine advise women to avoid their use during the lactation period.[61] Therefore, $H_1$ antihistamines should be used during lactation only when the need for their use overcomes the risks to the child. [61] Chlorpheniramine causes somnolence and reduction of the child's food intake. [61] The second-generation antihistamines loratadine and cetirizine can be used during the lactation period when needed, since only small amounts of these drugs are found in breast milk. [60,61]

*Breastfeeding children and preschoolers*

Hydroxyzine and chlorpheniramine are first-generation $H_1$ antihistamines authorized for use before two years of age. [61] Even though children can get used to the sedative effect of these drugs, there is a considerable risk of psychomotor block, which can have negative effects on the safety and education of children. [61] Desloratadine can be used in Europe and in the USA by children who are 1 year old or older. Fexofenadine and levocetirizine can only be prescribed for children between 1 and 2 years old, at the dose of 0.25mg/kg, divided in two daily intakes. [61]

*Elderly*

$H_1$ antihistamines are frequently used in the elderly for the treatment of rhinitis, conjunctivitis, pruritus, eczema and urticaria, in addition to prophylaxis of anaphylactoid reactions. [62] Second-generation $H_1$ antihistamines are excellent, effective, and safe alternatives to classical $H_1$ antihistamines in this age range. As with all medication, the choice of which drug to use should be made based on the needs of the patient. Treatment should be planned considering the drugs co-administered, the potential for drug interactions, and existing co-morbidities. First-generation $H_1$ antihistamines should not be used for the treatment of urticaria in the elderly. [62] Recently, Chen et al.[63] published a study about *potentially inadequate medication for the elderly* and concluded that $H_1$ antihistamines with anticholinergic and sedative effects are the most significant (first generation).

**Final considerations**

Most first-generation $H_1$ antihistamines inhibit CYP (essentially CYP2D6) and are capable of changing the metabolism of other drugs detoxified through this pathway, such as tricyclic antidepressants, beta blockers, antiarrhythmial drugs, and tramadol. [23] In addition, first-generation antihistamines cause well-known adverse effects, such as depression of cognitive functions and somnolence, among others. Low cost is one of their advantages compared to second-generation $H_1$ antihistamines.

Desloratadine, fexofenadine, cetirizine, levocetirizine, and rupatadine have cardiotoxic effects when their cytoplasmic levels increase because of interactions with other drugs or with fruit juice, both at the CYP3A4 level and gP and/or OATP family. [23] The wide availability of second-generation $H_1$ antihistamines in the public health system by competent authorities should be reevaluated due to their greater clinical safety in adults and children, the frequent need to associate various $H_1$ antihistamines at habitual doses to control CU [64], their posology comfort, and the existence of several generic pharmaceutical preparations in the Brazilian market. ❑

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How to cite this article/*Como citar este artigo:* Criado PR, Criado RFJ, Maruta CW, Machado Filho CA. Histamine, histamine receptors and antihistamines: new concepts. An Bras Dermatol. 2010;85(2):195-210.