Standard Treatment: The Role of Antihistamines

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Histamine-1 (H_1) antihistamines are the first-line drug for the treatment of urticaria. Major progress has been achieved in recent years both in the understanding of their ligands, the H_1-histamine receptors, and therefore in the mechanisms of their pharmacologic effects, as well as in the development of safer antihistamines with low or no sedating effects and no interactions on the level of potassium channels leading to QT-prolongations and interactions on the level of cytochrome P450 isoenzymes. This development has brought antihistamines very close to the ideal antihistamines that are desired by clinicians to treat most types of urticaria in patients who have to take these drugs for a long time. ***Key words: antihistamines/cytochrome P450/urticaria. Journal of Investigative Dermatology Symposium Proceedings 6:153–156, 2001***

Histamine-1 (H_1) antihistamines are the first-line drug for the treatment of urticaria. They all competively inhibit the binding of released histamine on H_1 receptors and thus decrease the incidence of wheals and the intensity of itching. The pharmacologist Holtz, who found that norepinephrine is a physiologic compound, once remarked: "What would be pharmacology without epinephrine, and what would be epinephrine without pharmacology." He underlined the importance of this compound for the understanding of ligand–receptor interactions for pharmacologic activities of small molecular weight compounds. Antihistamines play a similar role in dermatopharmacology and allergology as epinephrine plays in pharmacology. This is highlighted by the fact that Sir Henry Dale, who found that histamine alone can induce the triple response erythema, wheals, and itching, and Bovet, who developed the first antihistamine, were awarded the Nobel prize (Emanuel, 1999).

In recent years Yamashita *et al* have succeeded in cloning the gene encoding for the bovine H_1 receptor, and subsequently this sequence information was used to clone the H_1-receptor gene of humans, which is a protein of 487 amino acids (Chowdhury and Kaliner, 1996). This receptor belongs to the family of G protein coupled receptors, which is the largest receptor family, including more than 150 different receptors such as the histamine-1 and -2, the adrenergic, or the muscarinic acetylcholine receptors. Interestingly, in humans the H_1 receptor and the muscarinic acetylcholine receptor possess the highest sequence similarity of about 45% in the G protein coupled receptor family, which might explain the cholinergic-like side-effects of some antihistamines. The gene of the H_1 receptor is localized on chromosome 3 in humans and close to the gene of the interleukin 5α-receptor (Chowdhury and Kaliner, 1996; Leurs *et al*, 1996). G-protein-coupled receptors are characterized by seven transmembrane domains, which transverse the membrane in an α-helical configuration with three alternating extracellular and intracellular loops that connect the transmembrane region. The amino-terminal end of the receptor-protein is extracellular, the carboxy-terminal intracellular (**Fig 1**). The signaling pathway that is mediated by G proteins is dependent on a facilitated exchange of GTP for bound GDP after an agonist has bound to the receptor.

The binding of histamine to H_1 receptors in the skin induces the vascular endothelium to release nitric oxide, which stimulates guanyl cyclase and increases cyclic guanosine monophosphate in the vascular smooth muscle, which results in vasodilation, increased vascular permeability, edema formation, and erythema.

H_1-blocking agents generally share certain structural features. These include a substituted ethylamine moiety and a tertiary amino group linked by a two- or three-atom chain to two aromatic groups. Tricyclic derivatives exist in which the two aromatic rings are bridged. X is a nitrogen or carbon atom or a C-O ether bridge to the α-aminoethyl side-chain (Merk and Bickers 1992).

The H_1 antihistamines are widely used in dermatologic therapy for the symptomatic relief of the cutaneous manifestations of a variety of allergic disorders (Merk and Bickers 1992). These agents can be divided into several groups, as listed in **Table I**. In general, they have similar properties and the choice of an agent will depend on factors other than pharmacologic efficacy, including side-effects and cost. The effects of antihistamines in urticaria have been shown in numerous clinical studies (Sim and Grant, 1996; Simons, 2000; Simpson and Jarvis 2000; Tharp, 2000). The suppression of itching in urticaria is stronger than in other skin diseases with itching, such as atopic dermatitis (**Fig 2**) (Stüttgen, 1984; Henz *et al*, 1998). Their effect is limited, especially in pressure urticaria and severe forms of autoimmuneurticaria; however, after treatment of, for example, autoimmune urticaria with cyclosporine, antihistamines can be helpful in the case of a relapse of this condition (Grattan *et al*, 2000). In the treatment of cholinergic urticaria, antihistamines with a strong anticholinergic effect such as hydroxyzine may be helpful; however, apart from emergency cases in which antihistamines that can be given intravenously, such as clemastine or diphenhydramine, are used, today antihistamines without sedative effects are preferred (**Table II**).

SAFETY OF H_1 ANTIHISTAMINES

As antihistamines are often taken for long periods, the ideal antihistamine for urticaria should show high efficacy, no tachyphylaxis, and a good safety profile, with no cardiotoxic effects and no clinically significant drug interaction (Timmerman, 2000).

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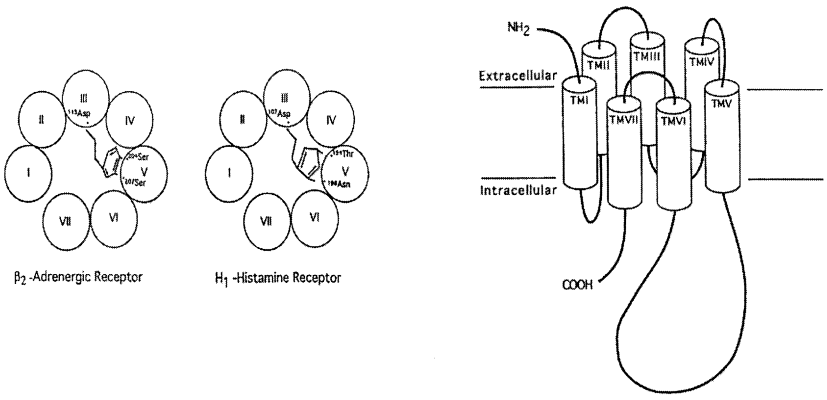

Figure 1. H_1 receptores belong to the G-protein coupled receptor family. (Adapted from Chowdhury and Kaliner, 1996.)

Table I. Major chemical groups of class 1 H_1 antihistamines

Ethylendiamines (e.g., pyrilamine)
Ethanolamines (e.g., diphenhydramine)
Alkylamines (e.g., chlorphehydramine)
Phenothiazines (e.g., promethazine)
Piperazines (e.g., cyclizine, hydroxyzine)
Piperidines (azatadine)

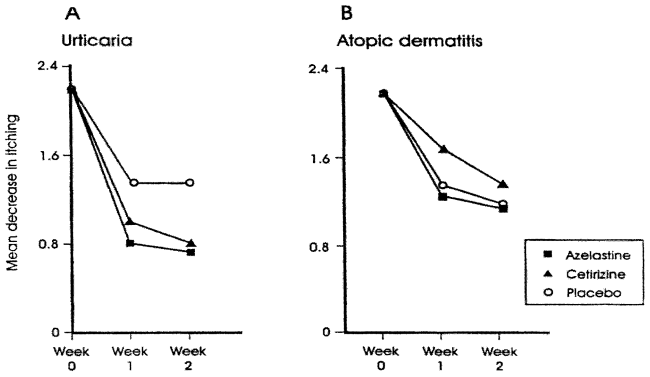

Figure 2. Antihistamines have a stronger effect on itching in urticaria than in other skin diseases such as atopic dermatitis. (Adapted from Henz *et al*, 1998.)

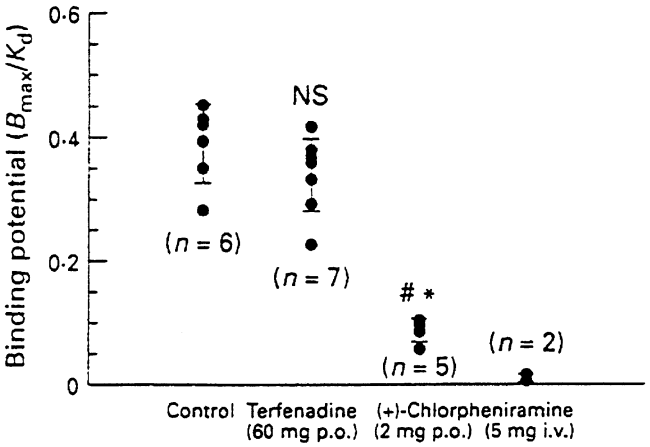

Figure 3. In this PET analysis of H_1-histamine receptors is the different effect by the nonsedating antihistamine terfenadine in comparison with the sedating antihistamine chlorpheniramine on CNS H_1 receptors shown. (Adapted from Yanai *et al*, 1995.)

Histamine functions as a neurotransmitter and it is particularly important in maintaining a state of arousal or awareness within the central nervous system (CNS) (Yanai *et al*, 1995). H_1 receptors are present in the CNS and they are especially expressed in the cerebral cortex, striatum, hypothalamus, olfactory tubercles, olfactory bulb, and pituitary gland (Chowdhury and Kaliner, 1996). Therefore the first, highly lipophilic antihistamines possess sedative effects as a major side-effect. This problem was overcome by the development of so-called second-generation antihistamines – terfinadine was the first one of them – that did not enter the CNS and therefore exerted no or markedly reduced sedative effects. These differencies between first-generation and second-generation antihistamines were elegantly demonstrated by PET studies, showing a reduced interaction of terfinadine and its metabolites with these CNS-located H_1 receptors (**Fig 3**) (Yanai *et al*, 1995).

Drug interactions between antihistamines and other drugs may occur on several different levels. Antihistamines with strong anticholinergic effects such as hydroxizine inhibit gastrointestinal motility, thereby reducing the rate of intestinal absorption of other drugs (Roos and Merk, 2000). Although the total amount of absorbed drug is not reduced, the retarded resorption of drugs such as analgesics can lead to a critical change in the distribution of a drug between neural and fat tissue and lowered therapeutic concentration. More attention was drawn to interactions of antihistimes and other drugs on the level of drug-metabolizing enzymes such as cytochrome P450 (CYP). The genes of these isoenzymes belong to a supergene family that is considered to be the largest known gene family. These enzymes metabolize small molecular weight compounds such as xenobiotica-including drugs. In humans most drugs are metabolized by the isoenzyme CYP3A4. In the case of terfinadine and astemizole an interaction on the level of CYP3A4-dependent metabolism was observed with, for example, ketoconazole, itraconazole, and erythromycin. This interaction can increase the concentration of terfenadine and thereby its interaction with the cardiac potassium channel leading to a QT-prolongation and the torsade-de-pointe arrythmias (Woosley, 1996). This particular problem was solved by the replacement of terfenadine by its metabolite fexofenadine, which acts as an antihistamine without having these problems. At this time fexofenadine and ceterizine – derived from hydroxyzine – are the two antihistamines that are not metabolized by CYP (Simpson and Jarvis, 2000). The metabolite of loratadine – desloratadine – will become available soon.[1] Many other antihistamines such as loratadine or mizolastine are also metabolized by CYP3A4, but as in these cases they can also be metabolized by other CYP-isoenzymes such as CYP2D6, and therefore an inhibition of CYP3A4 can be bypassed. Furthermore, loratadine does not have a

[1]Kreutner W, Hey JA, Anthes J, Barnett A, Tozzi S: Preclinical efficacy and antiallergic profile of desloratadine, a selective and nonsedating Histamine H_1-receptor antagonist. *J Allergy Clin Immunol* 105:382, 2000 (abstr.)

Table II. Examples of antihistamines that are used in chronic urticaria

Antihistamines	1× per day	Sedation	LA-activity	P450	Anti-inflammatory effect
Clemastin/Dimetidin	–	+	+	+	?
Terfenadin	–	–	+	+	+
Loratadin	+	–	– ?	+	+
Astemizol	+	–	+	+	?
Mizolastin	+	–	–	+	+
Ceterezin	+	– ?	–	–	+
Fexo-fenadin	+	–	–	–	+

similar interaction with the cardiac potassium channel as terfinadine.

Teratogenic effects have been noted in response to piperazine compounds, but extensive clinical studies have not demonstrated any association between the use of such antihistamines and fetal anomalies in humans (Garrison *et al*, 1990).

ANTIALLERGIC EFFECTS OF H_1-RECEPTOR ANTAGONISTS

When Bovet found the first compounds that possessed antihistamine-like activity, he was searching for drugs with anticholinergic activities, and several antihistamines also possess these. Therefore they are not H_1-receptor specific but only selective (Church *et al*, 1996). On the other hand signs and symptoms of allergic diseases including urticaria are not only mediated by histamine, and therefore it is of interest whether some antihistamines have more antiallergic activities than just the inhibition of histamine by preventing its binding to H_1 receptors. As early as 1953 it was reported that antihistamines might have the capability to inhibit the release of histamine from mast cells and basophils (Arunlakshana and Schild, 1953). Subsequent studies revealed that antihistamines are able to inhibit IgE-dependent release of histamines in low concentrations independently from their H_1-receptor antagonism, and that the lipophilicity of the antihistamines is a main factor that determines this effect. It has been suggested that the dissoving of the lipophilic end of the molecule in the cell membrane leads to the presentation of a positive charge on the outside of the cell membrane, this competetively inhibits the binding of calcium to the membrane, which subsequently reduces the calcium transport through the membrane, and therefore diminishes the activity of calcium-dependent enzymes such as calmodulin (Church *et al*, 1996). On the other hand, at high concentrations the expansion of the cell membrane increases by the solved antihistamines and this leads finally to an increase of histamine release. Therefore the concentration of the antihistamine under clinical conditions determines whether it inhibits or increases the histamine release from basophiles and mast cells, and this may differ from one antihistamine to another. There are several models that allow to determine this capability of antihistamines under clinical conditions (Nacliero and Baroody, 1996). One model are the physical urticaria, in particular the cold urticaria, because it is possible to induce this disease under experimental conditions. In one such experiment we studied four female patients aged 19–46 y with acquired cold urticaria of 1 mo to 24 y duration. The patients had been off all drugs for 7 d. On day 0, blood was taken from the antecubital veins and the hands were immersed in cold water at 5°C for 10 min. Further blood samples were taken 2, 5, 20, and 30 min after the end of the cold challenge for the histamine assay. From day 1 to day 7 ketotifen (2 mg per d) or oxatomide (60 mg per d) was taken. On day 7, 2 h after the last administration of the drug the cold challenge at the histamine assays were repeated. No drug was given on days 8–14 and on days 15–21 the alternative antihistamine ketotifen or oxatomide was administered. On day 21 cold challenge and histamine assays were performed once more. For the histamine assay, blood was taken and after centrifugation plasma was taken off and the histamine concentration was measured with a technicon analyzer after precipitation with 2 N perchloric acid. In all patients the histamine content increased after cold challenge on the side that was challenged with cold water compared with the nonchallenged side, and after the pretreatment with ketotifen or oxatomide the histamine concentration decreased. The mean value was 45.8% after ketotifen and 23.8% after oxatomide (Merk *et al*, 1985).

Beside its role as mediator of early onset type allergic reactions and promotor of gastric acid secretion, histamine is reported to modulate cellular and humoral immune responses (Sachs *et al*, 2000). It has been suggested with regard to certain diseases that are associated with increased histamine concentrations, like atopy or chronic gastritis, that histamine induces or promotes a shift from a Th_1 to a Th_2 immune response (Beer and Rocklin, 1987); however, the effects of histamine receptor antagonists on lymphocytes as the main actors in the immune response is only poorly understood (Munakata *et al*, 1999). Further effects on other cells or mediators that participate in inflammatory reactions such as eosinophils, adhesion proteins such as ICAM-1, or cytokines such as TNFα, interleukin 5, platelet activating factor, or leukotrienes, have been reported; however, their clinical significance at therapeutic concentrations of antihistamines remains controversial (Church *et al*, 1996).

Taken together the development of antihistamines (i) without influencing CNS effects of histamine and (ii) with no interactions on the level of the potassium channel of membranes with the risk of QT-prolongation as well as on the level of CYP-isoenzymes, has brought H_1 antihistamines very close to the ideal antihistamines which are desired by clinicians to treat most types of urticaria in patients who have to take these drugs for a long time.

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