PHARMACOLOGICAL PROPERTIES AND THERAPEUTIC USES OF ANTIHISTAMINES

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Antihistamines have played an important part in pharmacologic therapy for a wide variety of clinical conditions and they are among the most widely used medications in the world. This article will consider their mechanism of action and their clinical pharmacology, indications in dermatology and adverse effects. Three classes of histamine receptors have been identified: H^1 receptors, H^2 receptors which appear to stimulate gastric acid secretion, and H^3 receptors, which affect the central nervous system in a way that is not completely understood. We will discuss here H^1-receptor antagonists which include both the traditional first generation sedating antihistamines and the new nonsedating antihistamines.

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Action of Histamine:

Histamine is a potent mediator of a variety of physiologic and pathologic responses in different tissues and cells and is an important chemical mediator of inflammation in allergic disease [1]. It is synthesized by and stored in secretaroy granules of mast cells in a variety of tissues, most notably skin, lung, and gut [2]. It is also synthesized by and stored in circulating blood basophils [3]. Mast cell histamine is primarily a mediator in immediate hypersensitivity reactions whereas basophil-derived histamine is thought to contribute more to delayed hypersensitivity reactions. Histaminergic nerves have been identified in both the central and peripheral nervous systems [4]. However, the role of these nerves in inflammatory and anaphylactic reactions is not known. In humans, histamine is released immediately as a result of an antigen-IgE interaction on the surface of the mast cell during the immediate hy-

Table 1: THE ACTIONS OF HISTAMINE AT THE HISTAMINE RECEPTORS

System	H1 Receptor/s	H2 Receptors	H3 Receptors
Skin	Wheal, flare and itch		
Respiratory	Bronchial constriction Mucous Secretion	Bronchodilation Mucous Secretion	
Carido-vascular	Oedema due to increased capillary permeability Hypotension due to vasodilation of arterioles and precapillary sphincters Cardiac arrhythmia	Cardiac arrhythmia	
Gastro intestinal	Intestinal smooth muscle contraction	Gastric acid secretion	Inhibition of histamine Synthesis and release, inhibition of neurotransmitter release

persensitivity and allergic response. Following its release histamine induces bronchoconstriction of the airways and smooth muscle contraction of the gastrointestinal tract and plays an important part in causing pruritus and sneezing by sensory nerve stimulation. Such reactions are mediated via H^1 reactors and inositol phospholipid hydrolysis. Histamine induces vascular endothelium to release nitric acid, which stimulates guanylate cyclase and increases levels of cyclic guanosine monophosphate in vascular smooth muscle, causing vasodilation. By stimulation of H^1 and H^2 receptors, histamine causes hypotension, tachycardia flushing and headache. Activitation of H^2 receptors alone increases gastric acid secretion. H^3-receptors stimulation may have negative modulatory effects. The actions of histamine mediated by these receptors are listed in Table-1.

Mechanism of Action and Classification of Antihistamines:

Antihistamines are classified according to which receptor they block. Two different classes of antihistamines are currently available: H^1-blockers and H^2-Blockers [5]. More recently, the antihistamines that block H^1 receptors have been further classified according to their capacity to cause sedation into traditional or sedating antihistamines and new or nonsedating antihistamines. The traditional, first-generation H^1-receptor antagonists may also activate muscarinic cholinergic, 5-hydroxytryptamine (Serotonin) or alpha adrenergic receptors, whereas few of the second generation H^1 antagonists have any of these properties. The second generation, nonsedating antihistamines are considered more selective in their effect as they preferentially block the peripheral H^1 receptor sites with little or no effect on brain H^1 and cholinergic receptors. The low CNS toxicity of the second-generation nonsedating H^1 antagonists is probably due primarily to their inability to cross the blood brain barrier [6]. The new H^1 receptor antagonists are terfenadine and astemizole, which have been available since the mid 1980s and more recently loratadine, acrivastine and cetirizine have been available.

Table-2: PHARMACOLOGICAL PROPERTIES OF SOME ANTIHISTAMINES (H^1-BLOCKERS)

DRUG	Sedative activity	Anticholergic activity	Inhibitory activity on mast cell degranulation
Sedating Antihistamines:			
Antazoline	+	+	
Chlorpheniramine (Piriton)	+	+	
Clemastine (Tavegyl)	+	±	
Diphenhydramine (Benadryl)	++	+	
Hydroxyzine (Atarax)	++	++	
Ketotifen (Zaditen)	+	0	+
Mepyramine (Anthisan)	+	0	
Oxatomide (Tinset)	+	0	
Pheniramine (Avil)	+	+	+
Promethazine (Phenergan)	++	++	+
Triprolidine (Pro-Actidil)	+	0	
Non-Sedative Antihistamines:			
Acrivastine (Semprex)	0	0	
Astemizole (Hismanal)	0	0	
Cetirizine (Zyrtec)	0	0	0
Loratadine (Claritin)	0	0	+
Mequitazine (Primalan)	0	±	+
Terfenadine (Teldane)	0	0	+

Key: 0 = no effect = ± no effect or slight effect
+ = moderate effect ++ = marked effect

H^1 Receptor antagonists used to be classified according to their chemical structure but this conventional classification does not take into account the pharmacological differences that exist among drugs belonging to the same chemical entity. A prefered approach is to classify H^1-blockers according to their phar-

macological properties, such as the presence or absence of sedative or anticholinergic effects, or their ability to inhibit mast cell degranulation[5] *(Table 2)*

Table-3: PHARMACOKINETIC PROFILE OF REPRESENTATIVE H¹-RECEPTOR ANTAGONISTS:

H-RECEPTOR ANTAGONIST	TIME TO PEAK LEVEL (HOURS)	HALF-LIFE (HOURS)
First Generation		
Chlorpheniramine	2.8 ± 0.8	27.9 ± 8.7
Hydroxyzine	2.1 ± 0.4	20.0 ± 4.1
Diphenhydramine	1.7 ± 1.0	9.2 ± 2.5
Second Generation		
Terfenadine	0.78 -1.1	16 - 23
Terfenadine carboxylate	3	17
Astemizole	0.5 ± 0.2 to 0.7 ± 0.3	1.1 days
N-Desmethylastemizole	NA	9.5 days
Loratadine	1.0 ± 0.3	11.0 ± 9.4
Descarboethoxyloratadine	1.5 ± 0.7	17.3 ± 6.9
Cetirizine	1.0 ± 0.5	7.4 ± 1.6
Acrivastine	0.85 ± 0.14	1.4 - 2.1
Ketotifen	3.6 ± 1.6	18.3 ± 6.7
Azelastine	5.3 ± 1.6	22 ± 4
Demethylazelastine	20.5	54 ± 15

Pharmacological Properties of H1 Receptor Antagonists [5,7].

Antihistaminic Effects:

At low concentrations, H¹ antagonists are competitive antagonists of histamine. They bind to H¹ receptors but do not activate them, thereby preventing histamine from exercising some of its inflammatory effects. At higher concentrations, some second generation H¹ antagonists such as terfenadine, astemizole, and loratadine also exhibit non-competitive inhibition. The binding of most H¹ antagonists is readily reversible, but some of them such as terfenadine and astemizole, do not readily dissociate, from H¹ receptors[8]. Antagonists of this type provide potentially strong and prolonged protection against the effects of histamine on H¹ receptors.

Depressant effects on the Central Nervous System:

The traditional antihistamines cross the blood-brain barrier and bind to H¹ receptors in the CNS[9]. They can cause both CNS stimulation and depression resulting in sedation, the latter being the usual side effect limiting the clinical usefulness of these older H¹ antagonists. Central excitation is a striking feature of poisoning and can result in convulsions in infants. The newer H¹ antagonists do not significantly cross the blood-brain barrier when given in recommended therapeutic doses and hence have advantages in this aspect[10].

Anticholinergic (Antimuscarinic) Effects:

The ability of H¹-receptor antagonists to block responses mediated by muscarinic receptors is quite variable. Certain H¹-blockers e.g. terfenadine, astemizole, ketotifen, mepyramine and triprolidine may be regarded as being devoid of anticholinergic effects on muscarinic receptors when given in therapeutic doses[5]. In contrast, other compounds in this class such as brompheniramine, cyproheptadine, promethazine, dimenhydrinate, diphenhydramine or mequitazine, possess anticholinergic activity which may become clinically apparent in therapeutic doses. This activity may be useful for certain indications, but also responsible for adverse effects or contraindications[5].

Local Anaestehetic Effects:

Some H¹ antagonists, such as promethazine and mepyramine, possess local anaesthetic activity. However, the concentrations required for this effect are several times those required to antagonize histamine indicating perhaps a direct effect on histaminergic nerves with depolarization of efferent

nerve endings.

Action on Immunocompetent Cells:

Ketotifen, oxatomide, mequitazine, terfenadine and loratadine inhibit mast cell and/or basophil degranulation, as demonstrated by various experiments in animals and in humans [11]. H^1 antagonists have also been found to possess other properties, thus ketotifen inhibits the effects of platelet-activating factor (PAF) [12] and cetirizine exerts an inhibiting effect on eosinophil migration [13].

Pharmacokinetics of H1 Antagonists:

H^1-antagonists are well-absorbed after oral administration, often reaching peak plasma concentrations within two hours (Table 3) [14,15]. Protein binding ranges from 78 to 99 percent. Most H^1 antagonists are metabolized by the hepatic microsomal mixed function oxygenase system. Plasma concentrations are relatively low after single oral doses, which indicates considerable first-pass extraction by the liver, values for half-life in plasma are variable, for example, the half-life of chlorpheniramine is approximately 24 hours and that of active metabolites may differ from those of the parent compound; for example, astemizole has a half-life of 1.1 days, whereas its active metabolite, N-desmethylastemizole has a half-life of 5 days. The half-life of some H^1 antagonists may be shorter in children and prolonged in the elderly[16], patients with hepatic dysfunction [15], and microsomal oxygenase inhibitors[17]. Cetirizine, the active carboxylic acid metabolite of hydroxyzine, is not metabolized to any great extent in vivo, 60 percent of a dose is excreted unchanged in the urine within the first 24 hours. The half-life of cetirizine may be prolonged in patients with renal insufficiency. Acrivastine is also excreted mostly unchanged in the urine [17].

THERAPEUTICS USES OF ANTIHISTAMINES:

Antihistamines have been used to treat a wide variety of clinical problems and in particular in the areas of dermatology and E.N.T. The most common indications for antihistamines will be discussed in the following sections.

Angioedema, Acute and Chronic Urticaria.

Histamine is the best documented mediator of urticarial reactions and unquestionably urticaria is the primary indication for antihistamines in dermatology. Two thirds of patients respond to this treatment and the lack of response from the remaining third confirms the theory that other mediators are involved in the disease. The ideal management of an urticaria is to indentify and remove the precipitating cause. This is often possible in acute urticaria. Prompt treatment of the symptoms in both acute and chronic urticaria is obviously necessary until the precipitating factor is identified, and general advice on avoidance of known possible triggering factors is essential. Comparative studies have shown that both traditional antihistamines and the new, low-sedating H^1 antihistamines to be equally effective in the treatment of acute and chronic urticaria [18] H^1-antihistamines block binding of histamine to receptors and are therefore more effective in preventing the actions of histamine than in reversing any of its effects. For this reason the management of chronic urticaria is best achieved with regular prophylactic doses of antihistamines. The newer H^1 antagonists are safe and effective in the treatment of urticaria and because of their reduced sedating and anticholinergic side effects they are now the therapeutic agents of choice in the management of chronic urticaria. The nonsedating antihistamines, being devoid of anticholinergic effects, can be prescribed to patients with chronic bronchitis, prostatic adenoma, glaucoma or constipation and to patients taking anxiolytic drugs. The ideal H^1 antagonist for regular prophylactic treatment of urticaria should be orally active, have rapid onset, require only once-daily administration and have no unwanted effects (Tables-3 and Table-4). The first generation antihistamines are still useful when sedation is desired as in pruritus or when liquid preparations or parentral formulations of antihistamines are needed. In some patients with urticaria refractory to treatment with an H^1 antagonist alone, concurrent treatment with an H^2 antagonist such as Cimetidine or ranitidine enhances relief of pruritus and wheal formation [19,20]. In addition to a direct effect on H^2 receptors, which account for 10 to 15 percent of all histamine receptors on the vasculature, this effect may be due in part to the ability of some H^2 antagonist to inhibit the metabolism of H^1 antagonists in the hepatic cytochrome P-450 system, leading to elevated plasma and tissue concentration of H^1 antagonists [20]. How-

ever, the improved therapeutic efficacy of combined H^1 and H^2 Histamine antagonists in the management of refractory urticaria has not been observd by all investigators and the use of these combinations remains controversial. In practice, the addition of an H^2-blocker may be tried in the management of any urticaria that resists conventional treatments.

Atopic Dermatitis:

Although the evidence for a major role for histamine in atopic eczema is not strong, traditional H^1-blocker antihistamines have been used in the treatment of itching in atopic dermatitis for many years. The partial but unquestionable effect of these drugs in such a disorder seems to be due mainly to their sedative properties [21] and this appears to be confirmed by the fact that antihistamines devoid of effects on the central nervous system are less effective. Accordingly, one should prescribe products that possess a marked sedative effect, such as Diphenhydramine, hydroxyzine or promethazine to be taken at night. It must be borne in mind that in children who are predominantly affected by atopic dermatitis these drugs may give rise to paradoxical reactions of excitement and insomnia.

Anaphylaxis:

The initial drug of choice in patients with anaphylactic or anaphylactoid reactions is epinephrine (adrenaline), but H^1 antagonists are useful in the ancillary treatment of pruritus, urticaria, and angoiedema. They are also given prophylactically for anaphylactoid reactions to radiocontrast media and other substances. Unlike the traditional sedating antihistamine such as diphenhydramine, chlorpheniramine and hydroxyzine, the newer nonsedating anthistamines such as terfenadine and astemizole are not available in formulations for parenteral use for possessing low aqueous solubility. For anaphylaxis, H^2 antagonists are used concurrently with H^1 antagonists to reduce the effects of histamine on the peripheral vasculature and the myocardium [21].

Allergic Rhinoconjunctivitis and other upper Respiratory tract Disorders:

Antihistamines are highly beneficial in the management of nasal and ocular allergies. They appear to be more helpful for seasonal allergic and perennial allergic rhinitis than for nonallergic (vasomotor) rhinitis. H^1-antagonists prevent and relieve rhinorrhoea, sneezing, nasopharyngeal irritation and itching, lacrimation and red, irrititated or itching eyes [21]. When used without a decongestant, they are not directly effective in relieving symptoms of nasal obstruction but may do so indirectly, secondary to relieve of histamine-mediated irritation. In patients with allergic rhinoconjunctivitis, second-generation H^1 antagonists are comaparable in efficacy to each other and to first-generation H^1 antagonists such as chlorpheniramine. Although commonly used as "rescue" medications, H^1 antagonists are most effective if started before pollination begins and if used regularly during the pollen season [22]. The new topical H^1 antagonists levocabastine (Livostin) and azelastine have recently been introduced for the treatment of allergic rhinitis and conjunctivitis [23,24]. In contrast to their role in the treatment of allergic rhinitis, H^1 antagonists have little benefit in the treatment of upper respiratory tract infections and no benefit in otitis media [25].

Asthma:

Antihistamines have a proven, although mild, bronchodilatory effect. Pretreatment with an H^1 antagonist may provide some protection against bronchospasm induced by exercise and hyperventilation of cold or dry air. A classical example for the prophylactic use of antihistamines in asthma is ketotifen (Zaditen). General concerns about potential drying of secretions and worsening of asthmatic symptoms appear to be unfounded [17].

Other indications:

H^1-antagonists may be indicated for generalized pruritus associated with systemic disease, although the best approach is to treat the underlying systemic disease whenever possible. In biliary retention terfenadine was found to be significantly better than cholestyramine in the alleviation of itch[18].

Diphenhydramine (Benadryl) have proved useful in suppression of cough and in the treatment of tremor, muscle rigidity and drooling in patients with Parkinson's disease. Promethazine (Phenergan) and diphenhydramine have been recongnized as both safe and effective for self-medication as a sleep aid. However, tolerance to the sedative effect can result with prolonged use (longer than one week). First-generation antihistamines, which have a greater pro-

Table-4. Formulations and Dosages of Representative H[1]-Receptor Antagonists [21]

H1-Receptor Antagonist	Formulation	Recommended Dose*
First Generation		
Chlorpheniramine maleate	Tablets: 4 mg, 8 mg, 12 mg Syrup: 2.5 mg/ml Parenteral Solution 10mg/ml	Adult: 8-12mg2x/day Child 0.35mg/Kg/24 hr
Hydroxyzine Hydrochloride (Atarax)	Capsules: 10 mg, 25 mg, 50 mg Syrup: 10 mg/5 ml	Adult: 25-50 mg 2x/day or once a day, at bed time) Child: 2mg/Kg/24 hr.
Diphenhydramine Hydrochloride (Benadryl)	Capsules: 25 mg, 50 mg Elixir: 12.5 mg/5 ml Syrup: 6.25 mg/5 ml Parenteral solution: 50 mg/ml	Adult: 25mg 3x/day ChildL 5 mg/kg/24 hr.
Second Generation		
Terfenadine (Triludane)	Tablet: 60mg, 120mg Suspension: 30mg/5ml	Adult: 60mg 2x/day 120mg/day Child: 3-6 yr. 15mg 2x/day 7-12yr. 30mg 2x/day
Astemizole (Hismanal)	Tablet: 10mg Suspension: 10mg/5ml	Adult: 10mg. day Child: 0.2mg/Kg/day
Loratadine (Claritin)	Tablets: 10mg Syrup: 1mg/ml	Adult:10mg/day Child: 2-12 yr 5mg/day 12yr and 30 Kg 10mg/day
Cetirizine hydrochloride (Zyrtec, Reactine)	Tablets:10mg	Adult: 5-10mg/day
Acrivastine (Semprex)	Tablets: 8mg	Adult: 8mg 3x/day
Ketotifen fumerate (Zaditen)	Tablets: 1mg, 2mg Syrup: 1mg/5ml	Adult: with urticaria 4mg/day Child: 3yr. 1mg 2x/day
Azelastine hydrochloride (Astelin)	0.1% Nasal solution 0.137mg/spray	Topical: 2 sprays/nostril/day or 2x/day
Levocabastin hydrochloride (Livostin)	Micro suspension: 0.5mg/ml	Topical: 2 spray (50mcg/each)/ Nostril: 2-4 x/day or 1 drop (25mcg) in each eye 2-4x/day

* The dose for a child should be given if the patient weighs 40Kgs (90lbs) or less.

pensity to cross the blood-brain barrier have proved useful for the prevention and treatment of nausea, vomiting and/or vertigo associated with motion sickness, labrinthitis and Meniere's disease. The most widely used are dimenhydrinate (Dramamine) andmeclizine. Finally antihistamines have been used in the treatment of eating disorders and growth disturbances as appetite stimulants e.g. cyproheptadine (Periactin) and astemizole (hismanal).

Adverse reactions of H1 -Antagonists

The adverse effects of the classic first-generation H^1-antagonists on the central nervous system are the most frequently encountered in clinical practice. The drugs found to have the most pronounced sedative effect are promethazine, diphenhydramine and triprolidine. The least sedative are thought to be clemastine and chlorpheniramine [5]. The common sedative effects associated with first generation sedating antihistamines include somnolence, diminished alertness, slowed reaction time or impairment of cognitive function. The sedation induced by the classic antihistamines is potentiated by alcohol and central nervous system depressants. In very young children, these drugs may produce paradoxical CNS excitment.

The principal adverse effects related to the anticholinergic activity of H-receptor blockers include dryness of the mouth and pharynx, blurred vision, disorders of accomodation, closed-angle glaucoma, urinary retention, tachycardia and extrapyramidal reactions. Other side effects are gastro-intestinal upset and appetite stimulation. Jaundice, cytopenias and apnoea have been reported rarely. When H^1-antagonists are ingested in overdoses, they may produce coma, CNS stimulatory effects such as seizures, dyskinesia or neuropsychiatric effects such as hallucinations or psychosis. Cardiovascular adverse effects include palpitations, prolongation of the QTc interval and heart block[20]. Impairment of CNS function is reported to occur without experience of any symptoms and thus some older H^1-antagonists have been implicated as causes of fatal traffic accidents [26].

Topical use of H^1-antagonists had been associated with the development of severe sensitisation (e.g. phenothiazines) particularly when cutaneous erosions were present [27]. The newer second-generation H^1 -antagonists are devoid of the CNS sedative effects when used in therapeutic doses due to their inability to cross the blood-brain barrier. Most of the newer H^1-antagonists do not enhance the effects of alcohol and other CNS depressant drugs when administered with these agents. Astemizole and ketotifen like the first generation H^1-antagonist, cyproheptadine have been shown to stimulate the appetite and produce weight gain in some patients [20]. Astemizole and terfenadine have been reported on rare occasions to produce fatal or near fatal cardiac arrhythmias. Patients who are more prone to develop fatal ventricular arrhythmias include the elderly, patients with impaired hepatic function, those taking medications that cause prolongation of the QT interval or inhibit the metabolism of the antihistamines (e.g. the imidazole antifungal such as ketoconazole and itraconazole) or concomitant adminstration of macrolide antibiotics such as erythromycin and clarithromycin. The new topical intranasal antihistamines (azelastine and levocabastine) occasionally produce mucosal irritation, they do not induce sensitization during short-term topical therapy, in contrast to the dermal sensitization caused by the old H^1-antagonists.

Use of Antihistamines During Pregnancy and Lactation:

The definite safety of antihistamines during pregnancy is not guaranteed since human teratogenic data are either lacking or conflicting. Antihistamines fall into two pregnancy risk categories as defined by the U.S. Food and Drug Administration. These categories reflect both the extent of documentation and a risk: benefit ratio. The following antihistamines are in Category B (probably safe, with no toxicity noted in animal studies and/or no toxicity demonstrated in controlled studies in women): azatadine, cetirizine, chlorpheniramine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, doxylamine, loratadine, tripelenamine and triprolidine (Actidil).

Antihistamines associated with somewhat greater risk are those in Category C (adverse effects in animal studies, with no controlled studies in women available), including astemizole, brompheniramine, carbinoxamine, clemastin (Tavegyl), diphenhydramine, hydroxyzine (Atarax), pheniramine (Avil), promethazine (Phenergan) and terfenadine. Owing

to the increased risk of adverse reactions (e.g.seizures) in premature infants and neonates, it is prudent to avoid use of antihistamines in the third trimester of pregnancy.

Antihistamines show a wide variability in excretion into breast milk and most agents appear to have little data to confirm or refute potential adverse effects. Possible adverse effects include CNS stimulation, inhibition of lactation, respiratory depression, sleep apnoea and sudden infant death syndrome.

Loratadine, although excreted in breast milk in amounts equivalent to plasma levels was reported to be relatively safe during the breast feeding period [28]. At the present time, there is little data to suggest that antihistamines, when given in therapeutic doses, should not be given to nursing mothers.

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