

# Antihistamines and Their Role in Dermatology

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Antihistamines are valuable in treating skin disorders mediated by histamine. These are primarily used for the symptomatic relief of allergic reactions, such as urticaria and angioedema, rhinitis, conjunctivitis and pruritus associated with skin disorders. Antihistamines have also been found useful as tranquilizers, anticonvulsants, decongestants, local anesthetics, hypnotics and as antiparkinsonian<sup>1,2</sup> drugs. Many antihistamines cause some degree of sedation to which tolerance generally develops. Other adverse effects include antimuscarinic, extrapyramidal symptoms and hypersensitivity reactions. The newer antihistamines are less prone to cause sedation or antimuscarinic effects.

## **The role of histamine in dermatopathology**

The highest concentration of histamine is found in the lungs, skin and intestinal mucosa. Histamine is distributed widely in the animal kingdom and is found in venom, noxious secretions, bacteria and plants. Its main formation and storage occurs in mast cells but it is also found in epidermal, gastric mucosal cells, neurons within the central nervous system and in rapidly growing tissues<sup>3</sup>. Histamine produces a reaction known as the triple response. Erythema appears due to capillary expansion followed by a diffuse flare secondary to arteriolar dilatation. Lastly, a weal appears due to exudation of fluid through the altered vascular wall.

## **Tissue receptors**

The biological effects of histamine are the result of its interaction with H<sub>1</sub> and H<sub>2</sub> receptors. H<sub>1</sub> receptors mediate vasodilation, increased permeability of small blood vessels, smooth muscle contraction and itching. H<sub>2</sub> receptors are known for effecting gastric acid production. They also play a role in skin blood vessels and the immune system, somewhat resembling that of levamisole<sup>4</sup>. H<sub>3</sub> receptors are found in the brain and are responsible for autoregulation of histamine production and release<sup>5</sup>.

## **Classification of antihistamines**

H<sub>1</sub> and H<sub>2</sub> antagonists are different structurally, accounting for their differences in pharmacokinetic properties.

H<sub>1</sub> antagonists: These drugs are lipophilic. They show prominent sedation resulting in decreased attention, increased sleep duration and changes in EEG patterns. This occurs in fifty percent of subjects taking conventional antihistamines and in seven percent of subjects taking terfenadine or astemizole<sup>1</sup>. Antihistamines are readily absorbed from the stomach and small intestine, with peak blood concentrations in one to two hours. The newer agents such as, terfenadine, loratadine and astemizole are less lipid soluble and enter the central nervous system with difficulty or not at all. Their effective duration of action is four to six hours, but the newer H<sub>1</sub> blockers have a duration of 12 to 24 hours.

## **Ethanolamines**

Carbinoxamine (clistine): Antimuscarinic, central sedative and antiserotonin effects, 2-4 mg three to four times daily.

**Diphenhydramine (Benadryl):** Antimuscarinic, marked central sedation and antiemetic effects, 25-50 mg three to four times daily.

**Dimenhidrylate (Dramamine):** Antimuscarinic, marked central sedation, antiemetic effects, 50-100 mg three to four times daily.

**Clemastine (Tavegil):** Antimuscarinic with central sedative properties, 1 mg twice daily.

**Doxylamine (Decapryn):** Marked sedation; antimuscarinic effects; now available only in OTC "sleep aids".

**Ethylendiamines Antazoline (Antistine):** Component of ophthalmic and nasal drops as well, 50mg thrice daily.

**Pvriamine (Neo-Antergan):** Moderate sedation, component of OTC "sleep aids",

Tripelennamine (PBZ): 25-50mg daily. Antimuscarinic central sedation, 25-50 mg four to six hourly.

**Clernizole:** Moderate central sedation, 20-40 mg two to four times daily.

**Piperazines Cyclizine (Marzine):** Antimuscarinic, slight sedation, antiemetic, 50 mg thrice daily.

**Meclozine (Ancolan):** Antimuscarinic, slight sedation, anti-emetic, 25 mg twice daily.

**Bucizine (Longifene):** Antimuscarinic, marked sedation, antiemetic, 50mg upto thrice daily.

**Mebhydrolin (Incidal):** Antimuscarinic, sedation, 50-100mg thrice daily.

**Aikvlamines Triprolidine (Actidil):** Antimuscarinic, central sedation, 2.5-5 mg thrice daily.

**Pheniramine (Avil):** Antimuscarinic, central sedation. 25-50mg two to three times daily.

**Chlorpheniramine (Pinton):** Component of OTC "cold" medications, antimuscarinic, moderately sedating, 4mg four to six hourly.

**Phenothiazines Promethazine (Phenergan):** Antimuscarinic, marked central sedation 25mg at night.

**Trimethoprim (Vallergan):** Antiemetic, antimuscarinic, sedating, 10mg two to three times daily.

**Methdilazine (Tacaryl):** Antimuscarinic, sedating, 8mg two to four times daily.

**Ataraxis Hydroxazine (Atarax):** Antimuscarinic, sedating, anxiolytic, antiemetic, 25mg three to four times.

**Piperidines Astemizole (Mayasen):** Long acting with antiserotonin effect, no sedation or antimuscarinic activity, 10mg once daily.

**Terfenadine (Teldane):** No sedation, 60 mg twice daily.

**Miscellaneous Cyproheptadine (Periactin):** Antiserotonin, antimuscarinic, sedating, appetite stimulant, 12-16mg daily in three or four divided doses.

**Loratadine (Claritin):** Long acting, no sedation, 10mg once daily.

**Azatadine (Zadine):** Long acting, antiserotonin, sedating, antimuscarinic, 1 mg twice daily.

**Ketotifen (Zaditen):** Moderately sedating, appetite stimulant, mast cell stabilizing effects, 1 mg twice daily.

**Acrivastine (Semprex):** No sedation, 8mg thrice daily.

**Ebastine (No-sedat):** No sedation, 10mg once daily.

**Mequitazine (Metapiexan):** Minimal sedation, antimuscarinic 5 mg twice daily.

**Certrazine (Rigix, Zyrtec):** Long acting, minimal sedation, Additional anti-inflammatory actions and inhibitory effects on monocytes and T lymphocytes, 10mg once daily.

## **H<sub>2</sub> receptors blockers:**

These are highly hydrophilic, weak bases with variable lipophilicity. Ranitidine and cimetidine are the main H<sub>2</sub> blockers. Other drugs such as famotidine, nizatidine, roxatidine, niperotidine and investigational H<sub>2</sub> receptor antagonists have therapeutic effects similar to the above, but differ in potency and duration of action. They are rapidly and completely absorbed after oral ingestion. Their use in dermatology is quite modest. They may be of value in histamine mediated disorders which fail to respond to H<sub>1</sub> antagonists.

**Side effects of H<sub>1</sub> blockers:** Sedation is the most common side effect of these drugs. Other CNS effects may include dizziness, incoordination, blurred vision and diplopia. In certain instances, stimulatory effects such as nervousness, insomnia, tremor and irritability may occur. Gastrointestinal complaints associated with these drugs include nausea, vomiting, diarrhoea, constipation, anorexia and epigastric distress. Anticholinergic properties such as dry mucous membranes, difficulty in micturition, urinary retention and impotence can be disturbing. The cardiovascular effects like hypotension usually follow intravenous therapy, especially when given rapidly. Cutaneous reactions occurring after administration of H<sub>1</sub> blockers include fixed drug eruptions, petechial rashes, urticaria, photosensitivity and eczematous contact dermatitis. The latter usually occurs with topically applied antihistamines. Systemic administration of an antihistamine to which there has been topical sensitization will not only

reproduce the original allergic contact dermatitis, but at times, a generalized exfoliative dermatitis<sup>8</sup>. On rare occasions, parenteral administration can result in morbilliform and scar—letiform eruption and anaphylactic shock.

Theoretically all antihistamines can be teratogenic in animals and therefore should be avoided in pregnancy<sup>9</sup>. The dyes used in the outer coating of tablets can give rise to allergy like idiosyncratic reactions. Terfenadine and astemizole have been associated with QT interval prolongation and ventricular arrhythmias. Therefore, caution is advised in patients with existing repolarization abnormalities and those at risk of elevated levels of antihistamines<sup>10</sup>.

### **Drug interactions of H1 antagonists**

These can potentiate the effects of alcohol and other CNS depressants including hypnotics, anxiolytic, sedatives, opioid, analgesics and tranquilizers. The actions of CNS stimulants can be enhanced in children and infants. H1 blockers antagonise the effectiveness of steroids, diphenhydantoin, oral anticoagulants, phenylbutazone, griseofulvin and other drugs metabolized by liver enzymes. Significant cardiac toxicity has occurred in patients taking a combination of either terfenadine<sup>11,12</sup> or astemizole<sup>13</sup> and ketoconazole, itraconazole or erythromycin. The anticholinergic activity of antihistamines is potentiated by anticholinergic drugs.

### **Side effects of H2 antagonists:**

These drugs are usually well tolerated. Cimetidine has been associated with diarrhoea, headache, dizziness, drowsiness, malaise, muscular pains, constipation, gynecomastia, galactorrhea, loss of libido, impotence and reduction of sperm counts in young men<sup>14</sup>. This resolves after the drug is discontinued. Due to its antiandrogenic activity and reduced sebum secretion, generalized xerosis and asteatotic dermatitis has been reported<sup>15</sup>. Psoriasis has been reported in an 86 year old woman during her treatment with cimetidine for duodenal ulcer<sup>16</sup>. Urticarial vasculitis, alopecia, hypersensitivity and induction or exacerbation of lupus erythematosus has been reported with cimetidine<sup>13</sup>. Reversible elevation of serum transaminases and granulocytopenia can occur. Symptoms of gastric carcinoma may be masked with cimetidine<sup>17</sup>. Cimetidine and to a lesser extent, ranitidine can inhibit the cytochrome P450 oxidative drug metabolizing system. Both drugs inhibit the renal clearance of basic drugs.

### **Drug interactions of H2 antagonists**

Due to inhibition of metabolism of drugs, cimetidine can prolong the pharmacological activity of diazepam, chlorthalidone, warfarin, theophylline, propranolol, phenytoin, caffeine, alprazolam, tricyclic antidepressants, carbamazepine, calcium channel blockers and sulphonylureas. Ranitidine in ordinary therapeutic doses, does not appear to inhibit the oxidative metabolism of other drugs. Clinically significant drug interactions have not been reported with famotidine and nizatidine<sup>1</sup>. Therapeutic uses of antihistamines in dermatology

They are mainly used for the symptomatic relief of pruritus and treatment of urticaria and angioedema. A trial of H1 antagonists especially at bed-time is helpful for the symptomatic relief of itching. Initially chlorpheniramine (4mg) or hydroxyzine (10-25 mg) by mouth is prescribed. Atopic dermatitis is more responsive to sedating antihistamines such as trimeprazine as compared to non-sedating ones such as terfenadine or astemizole<sup>18</sup>. These have to be combined with the relevant topical therapy such as emollients, steroids or tar. Sedation is desirable in the treatment of atopic dermatitis as its itching involves a central component.

Psychogenic pruritus benefits from antidepressant therapy with doxepin or sedative therapy with hydroxyzine which has anxiolytic effects as well<sup>19</sup>. In the allergic dermatoses, benefit is most striking in acute urticaria although the itching is better controlled than the erythema and oedema<sup>3</sup>. Hydroxyzine is commonly used in the treatment of urticaria. It is also useful in suppressing histamine induced pruritus in dermographism and in cholinergic urticaria<sup>20,21</sup>. Cyproheptadine and pheniramine have been

found to be slightly more effective than chlorpheniramine and hydroxyzine in aquagenic urticaria<sup>22</sup>. Cyproheptadine is often the drug of choice in patients with acquired cold urticaria/angioedema<sup>23</sup>. The non-sedating antihistamines acrivastine<sup>24</sup>, astemizole<sup>25</sup>, cetirizine<sup>25</sup>, loratadine<sup>26</sup> and terfenadine<sup>27</sup> have been found to be effective in chronic urticaria. Comparative studies have generally shown no clear difference in their efficacy. The mast cell stabilizing H1 antagonists such as ketotifen and azatadine have shown efficacy in the treatment of urticaria<sup>13</sup>.

H1 antihistamines have shown improvement in contact dermatitis, infestations and pruritus secondary to underlying idiopathic disorders. Topically, H1 antihistamines notably diphenhydramine are effective analgesics particularly on mucous membranes<sup>1</sup>. H1 antagonists can be used as adjuvants in anaphylactic reactions as they act against the urticarial and angioedematous responses; but do not control the associated hypotension and bronchospasm. In acute anaphylactic reactions, adrenaline is given subcutaneously followed by intravenous hydrocortisone, if necessary.

The combination of H1 and H2 antagonists can be considered in patients in whom H1 antihistamines alone are ineffective. Cimetidine or ranitidine, administered alone or in combination with an H1 receptor antagonist have shown benefit in certain types of urticaria, especially those associated with cold or angioedema<sup>28</sup>. Routine use however, cannot be justified. Cimetidine alone or in combination with an H1 antagonist has been reported to relieve the gastrointestinal symptoms<sup>29,30</sup> pruritus and urticaria<sup>31,32</sup> in mastocytosis. Cimetidine has been found useful in treating the pruritus of Hodgkin's disease<sup>33</sup> and polycythemia vera<sup>34</sup>.

The antiandrogenic effect of cimetidine has produced favourable results in hirsutism<sup>35</sup>. However, in a recent study, it was concluded that its weak antiandrogenic action was insufficient for it to effectively treat hirsutism<sup>36</sup>. H2 receptor antagonists have been used as immune stimulants in chronic fungal infections<sup>37</sup>. Cimetidine has unpredictably caused both remission<sup>38</sup> and lack of response<sup>39</sup> in eosinophilic fasciitis. There have been reports of cimetidine producing clinical improvement and sometimes complete remission in malignant melanoma when used in combination with coumarin<sup>40</sup> interferon<sup>41</sup> or topical diphenylpicrylhydrazine<sup>42</sup>. However, response to the latter treatment modalities is not predictable. Some patients do not respond and in some there may be progression of disease.

## Conclusion

Antihistamines are an important therapeutic class of drugs that are useful in many conditions. It is suggested that if there is lack of clinical response or side effects, a representative from another group should be tried. Effects other than H1 or H2 receptor blocking are not necessarily undesirable, and in some cases may improve efficacy. Tolerance to sedation often develops. The recent introduction of relatively non-sedating antihistamines has made it essential to understand, what one is attempting to achieve, a central or a peripheral effect.

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