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REVIEW (CPD)

An overview of anti-allergic drug therapy and the histamine-1 antihistamines

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Abstract

Allergic disease decreases the daily quality of life of many people, and can increase the number of working days lost owing to sick leave. Associated symptoms with allergic disease depend on the origin of the disease, and can either be allergic, non-allergic and purulent, or can cause rhinitis as a result of a common cold. Treatment depends on the origin of the rhinitis. However, an antihistamine is indicated in most instances. Combination treatment includes sympathomimetic drugs (either local or systemic) and corticosteroid medication (when indicated, and in most instances, used locally). The article provides an overview of the nature and the management of allergic disease and the histamine 1 antihistamines.

Keywords: anti-allergic drug therapy, H_1 antihistamines, histamine receptors, allergic rhinoconjunctivitis, allergy health

Introduction

Acute allergic reactions and anaphylaxis are mediated by histamine release from degranulated mast cells. Histamine, in combination with other vasoactive substances, such as bradykinin, serotonin, prostaglandins and leukotrienes, causes glottis oedema; bronchospasm; increased capillary permeability and vasodilatation with a subsequent drop in arterial blood pressure; skin signs, such as blushing, pruritus and urticaria; as well as gastrointestinal symptoms, such as cramping, nausea, vomiting and diarrhoea.[1-3]

Histamine is an interesting and important signal transmitter substance since it acts both as a neurotransmitter within the central nervous system (CNS) and as an important autacoid within peripheral tissue, a characteristic that it shares with serotonin. Histamine is synthesised from the amino acid, histidine.[1-3]

Peripherally, histamine is stored in a bound and inactive form within the storage vesicles or granules of mast cells in tissue and the basophils in the bloodstream. Mast cells have a highly predictable distribution pattern inside the human body since they serve to protect open-ended organ systems. These organ systems, being "open" to the external environment, contain an abundance of these cells. They are the open-ended tracts of the respiratory and gastrointestinal systems.[1-3]

The obvious exposure of the skin to the external environment also explains the abundance of mast cells found on it, especially in areas that readily blush. Histamine is also secreted in the fundus of the stomach, where its function is to interact with histamine-2 (H_2) receptors, and thereby stimulate the secretion of gastric acid by the stomach's parietal cells.[1-3]

Histamine is a particularly important mediator of the inflammatory process. This process, as a pathophysiological entity, is activated within peripheral tissue areas when mast cell degranulation occurs. This degranulation may be triggered in the following ways:[1-3]

- Physical trauma of the tissue cells in question
- An interaction between immunoglobulin E (IgE) antibodies and suitable IgE antigens, i.e. the formation of antigen-antibody complexes that cause allergic reactions (localised histamine release) or anaphylaxis (systemic histamine release)
- Exposure to snake and wasp venom
- Large molecules, such as those found in the serum of animals, e.g. equine serum, or the rather large molecules of dyes and alkaloid bases, such as morphine, and the depolarising skeletal muscle relaxants, such as tubocurarine and atracurium.

Of the four currently identified histaminergic receptor subtypes, i.e. the H_1-H_4 receptors, the H_1 receptor is especially well known for its active role in mediating acute allergic reactions. Some of the effects of H_1-receptor stimulation include allergic rhinitis and conjunctivitis, urticaria, pruritus (histamine stimulates sensory neurons to produce itching) and angioneurotic oedema.[1-3]

Stimulation of these receptors is also responsible for the vasodilatation and the increased vascular (capillary) permeability that accompanies allergic reactions and inflammation. Erythema and oedema, including potentially fatal glottis oedema, may ensue. Blood pressure may be decreased to such an extent that anaphylactic shock sets in. Bronchial smooth muscle contraction causes bronchoconstriction, with wheezing and possible bronchospasm. The contraction of gastrointestinal smooth muscle results in colic. Exocrine gland secretions are increased through H_1-receptor stimulation.[1-3]

Histamine acts as an excitatory neurotransmitter within the CNS, via H_1-receptor activation. Therefore, antagonists at these central H_1 receptors cause somnolence and sedation. In addition, the emetic or vomiting centre in the medulla oblongata also

contains H_1 receptors, in which case receptor antagonism results in an antiemetic effect.[1-3]

Allergic rhinoconjunctivitis

An allergy may be viewed as a hypersensitivity disorder of the immune system. Jointly, allergies constitute the fifth leading group of chronic diseases worldwide. The broader name, allergic rhinoconjunctivitis (the involvement of the eyes and nose), is not that well known, and is commonly referred to as allergic rhinitis. Allergic rhinitis presents with nasal symptoms of congestion and rhinorrhoea, and is more commonly associated with complaints of ocular symptoms.[4-7]Allergic conjunctivitis is an inflammatory response of the conjunctivae to allergens, such as pollen (grass), environmental antigens (dust) and animal dander.[4,5,7-9]

Allergic rhinoconjunctivitis may be an acute or chronic illness, and is typically classified as being either seasonal or perennial, based on the type of allergen and the occurrence of symptoms during the course of the year. Seasonal rhinoconjunctivitis usually occurs during the spring and autumn, when levels of outdoor allergens (pollen) are elevated, whereas perennial rhinoconjunctivitis is present throughout the year, is more chronic in nature and is caused by indoor allergens, e.g. pets, dust mites and cockroaches.

However, more recently this classification was revised by the Allergic Rhinitis and its Impact on Asthma workshop. The new classification does not consider the type of allergen, but rather involves the duration of symptoms and their subsequent impact on a person's quality of life. Furthermore, the revision now differentiates between either intermittent (not more than four weeks in duration) or persistent (more than four weeks in duration) allergic conjunctivitis or rhinitis.[4,10]

The most common antigens for allergic rhinitis are inhalant allergens, of which dust mites, animal dander and pollen cause the most concern. When a patient is sensitised, an antigen comes into contact with the nasal mucosa. This leads to cross-linking of IgE-mediated receptors on the mast cells. This, in turn, leads to degranulation of the mast cells, with a resultant release of histamine and proteases from the preformed granules. In addition, an array of early-phase proinflammatory molecules are synthesised and released, especially prostaglandins, leukotrienes, cytokines, tumour necrosis factor (TNF)-alpha (TNF-α) and interleukin (IL)-4. The release of these molecules causes oedema and fluid secretion, resulting in congestion and other nasal symptoms. The role of leukotrienes as mediators in allergic rhinitis is well supported in the literature. Cysteinyl leukotrienes are able to facilitate the maturation of eosinophil precursors and act as eosinophil chemoattractants, promoters of eosinophil adhesion and inhibitors of eosinophil apoptosis. The leukotrienes and thromboxane A_2 (TXA_2) are arachidonic acid derivatives, and it has been shown in animal models that TXA_2 agonists increase nasal airway resistance and vascular permeability. An acute-phase allergic reaction is also characterised by the production of prostaglandin D_2 (PGD_2), a major proinflammatory prostanoid, which results in vasodilation and bronchoconstriction, as well as a number of inflammatory biomarkers, such as N-alpha-tosyl L-arginine methyl ester (TAME)-esterase and eosinophil cationic protein (ECP). PGD_2 is also believed to be associated with hypertrophic inflammation and acts as a recruiter of eosinophils.

The late-phase or chronic inflammatory response involves cellular infiltration, which sustains tissue swelling and oedema, and further exacerbates congestion. The ensuing cytokine release results in the nasal mucosa being infiltrated with inflammatory cells. These inflammatory cells, including eosinophils, neutrophils, basophils, mast cells and lymphocytes, sustain and intensify the nasal mucosal inflammatory reaction. The predominant cell type, the eosinophil, characterises the chronic inflammatory process that is present during the late-phase allergic response. These eosinophils release a broad range of proinflammatory mediators, including the cysteinyl leukotrienes, ECP, eosinophil peroxidase and major basic protein. These cells are also known to serve as a major source of IL-3, IL-5, granulocyte-macrophage colony-stimulating factor and IL-13. The number of circulating eosinophils is increased in patients with allergic disorders, and infiltration at the site of aggravation has been generally attributed to the influx of mature cells. In some studies, eosinophil infiltration has been shown to have a significantly negative correlation with nasal airflow in patients with allergic rhinitis. In addition to the eosinophils, other proinflammatory cells are also known to accumulate within the nasal epithelium during the late-stage response. These include basophils, mast cells and T cells. The key inflammatory mediator

Table I: A summary of the different types of rhinitis and their associated management strategies

Rhinitis associated with a common cold	Purulent rhinitis	Allergic rhinitis	Non-allergic rhinitis (vasomotor rhinitis)
• Steam inhalations • Systemic decongestants • Local decongestants	• When associated with sinusitis, antibiotics may be needed • Nasal decongestants • Nasal irrigations with saline • Check for a foreign body in the nose in children	• Avoidance of the allergen wherever possible • Systemic antihistamines, where needed • Topical corticosteroids: As prophylaxis, they should be started two weeks prior to the allergy season and continued until the season is over • Systemic corticosteroids • Local decongestants • Hyposensitisation with allergen-specific immunotherapy	• Avoid precipitating factors • Short-term topical decongestants may be used when necessary

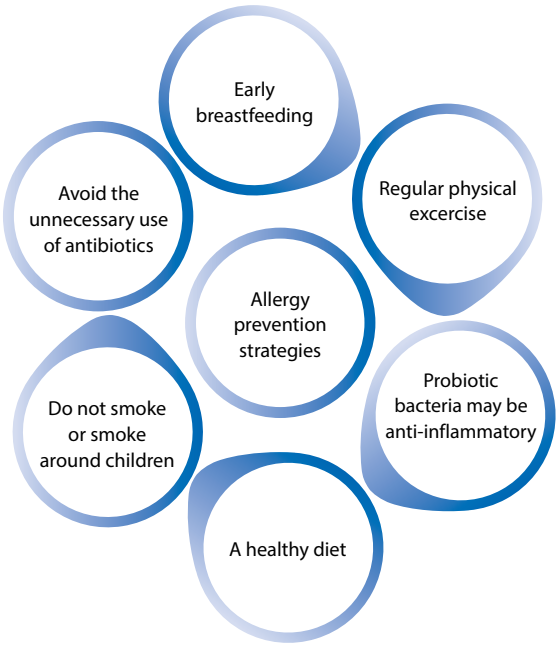

Figure 1: Prevention strategies in the management of allergy disease

of the late-phase response is TNF-α, and TNF-α levels increase dramatically roughly an hour after an allergen challenge. This cytokine has been confirmed to activate T cells, endothelial cells, fibroblasts and macrophages. TNF-α is also responsible for an increase in the expression of cell adhesion molecules. Patients with allergic rhinitis also have elevated proinflammatory interleukins (IL-1β, IL-6 and IL-8). All of these events, including IgE synthesis and eosinophil or basophil priming, contribute to the venous engorgement, inflammation, nasal and ocular hyper-reactivity and symptoms of allergic rhinoconjunctivitis.[4,5,10-16]

The symptoms that are associated with allergic rhinoconjunctivitis due to an IgE-mediated inflammatory response include nasal symptoms, such as congestion, nasal itching, sneezing and rhinorrhoea; and ocular symptoms, such as itching, redness, watering or tearing and burning. These symptoms are frequently reported by allergic rhinitis patients, and are more prominent in patients experiencing seasonal allergic rhinitis.

The symptoms of allergic rhinitis can affect patients' quality of life, including a reduction in sleep quality, the performance of daily activities, cognitive function, work productivity and examination performance. These symptoms also have an impact on patients' psychosocial well-being.[7,10,13,15,16]

Practical actions to promote allergy health

Certain behavioural activities have been shown to provide some protection against, or may alleviate some of the symptoms derived from, a current allergic reaction. Other practical interventions include prevention strategies (Figure 1.)[17] These strategies may improve immune tolerance. However, the benefits of probiotics in either preventing or treating allergic disease remain inconclusive.[17]

The prevention strategies identified in Figure 1 may be combined with more specific management principles according to the type of rhinitis that the patient is experiencing.[2,18] The difference between allergic rhinitis and non-allergic rhinitis may be explained by the presence of precipitating factors. Allergic rhinitis may be induced by IgE-mediated inflammation of the nasal mucous membranes. The patient may present with nasal (sneezing, nasal obstruction or congestion, and rhinorrhoea or postnasal drip and congestion) and non-nasal symptoms (an itchy palate or ears, and conjunctivitis). Non-allergic rhinitis may present with symptoms relating to a physiological response to heat, smoke, cold and dust.[2,18,19] Table I provides a summary of the different types of rhinitis and their associated management strategies.

Medicine management of allergic diseases

Nonpharmacological strategies, as well as pharmacological strategies, can be used in the management of allergic diseases. If nonpharmacological strategies do not alleviate the condition, then the following pharmacological agents may be used, either topically or systemically, for the prevention and management of allergic disease.[4] Table II consists of over-the-counter pharmacological preparations that are available to manage allergic diseases.[18,20]

Local decongestants

These agents contain sympathomimetic drugs, like xylometazoline, oxymetazoline and phenylephrine.[2,18,21] They produce vasoconstriction via α_1-adrenergic receptor stimulation. This, in turn, reduces mucosal oedema and local vasodilation. Nevertheless, these effects only last for a limited period. After prolonged use, rebound rhinitis and conjunctivitis or conjunctivitis medicamentosa may set in, usually after roughly five days of continuous use. Oxymetazoline and xylometazoline have a long-acting effect on the α_1 receptor, whereas phenylephrine has a shorter-acting effect, lasting up to approximately four hours.[4,18,19,21]

Systemic decongestants

Many of these preparations also contain antihistamines. The antihistamines have an antagonistic effect on histaminergic H_1 receptors. This will be discussed in the subsequent section. Pseudoephedrine, phenylpropanolamine and phenylephrine are available systemic decongestants in South Africa. These agents produce vasoconstriction through α_1-receptor stimulation, reducing oedema, redness and itching. However, the combination of a systemic decongestant and an older-type H_1 antihistamine may produce drowsiness and a lack of coordination. The use of phenylpropanolamine produced subarachnoid bleeding with a haemorrhagic stroke in women who used it as an appetite suppressant. The total daily dosage of phenylpropanolamine should not exceed 100 mg.[4,18,19,21]

Local corticosteroids

Glucocorticosteroids modify protein synthesis directly by regulating transcription, and indirectly by altering the activity or half-life of the transcription factors and mRNA. The following intranasal corticosteroids are currently available: beclomethasone, budesonide, fluticasone, mometasone, triamcinolone and ciclesonide. Intranasal administration of the newer agents, mometasone, fluticasone, and ciclesonide, results in minimal systemic effects.[22] The most common local side-

Table II: Over-the-counter medications used for allergic rhinitis

Preparation	Active ingredients	Indications	Price
Local decongestants			
Iliadin®	Oxymetazoline (0.100 mg/ml)	Short-term symptomatic relief of nasal congestion	R31.90
Drixine®	Oxymetazoline (0.5 mg/ml)	Short-term symptomatic relief of nasal congestion	R32.26
Nazene Adult®	Oxymetazoline (0.5 mg/ml)	Short-term symptomatic relief of nasal congestion	R35.99
Otrivin®	Xylometazoline (1 mg/ml)	Short-term symptomatic relief of nasal congestion	R53.71
Sinutab nasal spray®	Xylometazoline (1 mg/ml)	Short-term symptomatic relief of nasal congestion	R35.00
Vibrocil-S®	Phenylephrine and dimethindene (250 mg/100 g)	Short-term symptomatic relief of nasal congestion	R37.19
Local corticosteroids			
Avamys	Fluticasone Furoate	Maintenance therapy for allergic rhinitis	R165.81 (120 metered sprays)
Beclate Aquanase®	Beclomethasone dipropionate (50 µg/spray)	Maintenance therapy for allergic rhinitis	R55.70
Beconase®	Beclomethasone dipropionate (50 µg/spray)	Maintenance therapy for allergic rhinitis	R107.66
Clenil AQ Nasal Spray®	Beclomethasone dipropionate (50 µg/spray)	Maintenance therapy for allergic rhinitis	R51.35
Flomist®	Fluticasone propionate(50 µg/spray)	Maintenance therapy for allergic rhinitis	R73.92
Flonase®	Fluticasone propionate (50 µg/spray)	Maintenance therapy for allergic rhinitis	R68.40
Nexomist®	Mometasone furoate (50 µg)	Maintenance therapy for allergic rhinitis	R170.74
Rinelon®	Mometasone furoate (50 µ)	Maintenance therapy for allergic therapy	R74.81 (60 metered sprays) R174.57 (140 metered sprays)
Topical antihistamines or antiallergic agents			
Rhinolast®	Azelastine (0.14 mg/spray)	Short-term intermittent allergic rhinits	R51.30
Sinumax allergy nasal spray®	Levocabastine (0.5 mg/ml)	Short-term intermittent allergic rhinitis	R69.51
Vividrin®	Cromoglicic acid (2.6 mg/spray)	Intermittent or persistant allergic rhinitis	R34.58
Other nasal preparations			
Mistabron®	Mesna (50 mg/ml)	Nasal obstruction due to thick secretions	R101.97
Systemic nasal decongestants with antihistamines			
Actifed®	Pseudoephedrine HCl (30 mg) Triprolidine HCl (1.25 mg)	Systemic decongestion of nasal mucosa and sinuses associated with colds and flu	R19.54
Betafed Be-Tabs®	Pseudoephedrine HCl (30 mg) Triprolidine HCl (1.25 mg)	Systemic decongestion of nasal mucosa and sinuses associated with colds and flu	R17.05
Demazin Syrup®	Phenylephrine HCl (2.5 mg/5ml) Chlorpheniramine (1.25 mg/5 ml)	Systemic decongestion of nasal mucosa and sinuses associated with colds and flu	R39.52
Demazin NS®	Pseudoephedrine sulphate (120 mg) Loratidine (5 mg)	Systemic decongestion of nasal mucosa and sinuses associated with colds and flu	R26.51
Systemic decongestant and/or analgesic and/or antihistamine combinations			
Nurofen cold & flu®	Ibuprofen (200 mg) Pseudoephedrine HCl (30 mg)	Symptomatic relief of colds and flu	47.66
Sinuclear®	Paracetamol (325 mg) Phenylpropanolamine HCl (18 mg)	Symptomatic relief of colds and flu	R33.61
Sinugesic®	Paracetamol (500 mg) Pseudoephedrine HCl (30 mg)	Symptomatic relief of colds and flu	R22.54
Sinumax®	Paracetamol (500 mg) Pseudoephedrine HCl (30 mg)	Symptomatic relief of colds and flu	R45,31
Sinustat®	Paracetamol (325 mg) Phenylpropanolamine HCl (18 mg)	Symptomatic relief of colds and flu	R21.16
Sudafed sinus pain®	Paracetamol (500 mg) Pseudoephedrine HCl (60 mg)	Symptomatic relief of colds and flu	R14.23

Table II: Over-the-counter medications used for allergic rhinitis

Antihistamines			
Acuzyrt®	Cetirizine dihydrochloride (10 mg)	Symptomatic treatment of allergic conditions	R50.16 (30 tablets)
Adco-Cetirizine®	Cetirizine dihydrochloride (10 mg)	Symptomatic treatment of allergic conditions	R61.83 (30 tablets)
Allecet®	Cetirizine dihydrochloride (10 mg)	Symptomatic treatment of allergic conditions	R52.03 (30 tablets)
Preparation	**Active ingredients**	**Indications**	**Price**
Sinutab Sinus Allergy®	Cetirizine dihydrochloride (10 mg)	Symptomatic treatment of allergic conditions	R18.25
Texa Allergy®	Cetirizine dihydrochloride (10 mg)	Symptomatic treatment of allergic conditions	R55.07 (30 tablets)
Zyrtec®	Cetirizine dihydrochloride (10 mg)	Symptomatic treatment of allergic conditions	R144.14
Allergex®	Chlorpheniramine maleate (4 mg)	Management of allergic disorders	R34.29 (30 tablets)
Rhineton®	Chlorpheniramine maleate (4 mg)	Management of allergic disorders	R137.42
Allergex Non Drowsy®	Loratadine (10 mg)	Symptomatic treatment of allergic conditions	R39.65 (30 tablets)
AP Loratadine®	Loratadine (10 mg)	Symptomatic treatment of allergic conditions	R46.90 (30 tablets)
Cipla-Loratadine®	Loratadine (10 mg)	Symptomatic treatment of allergic conditions	R47.33 (30 tablets)
Clarinese®	Loratadine (10 mg)	Symptomatic treatment of allergic conditions	R15.61 (10 tablets)
Luara®	Loratadine (10 mg)	Symptomatic treatment of allergic conditions	R44.18 (30 tablets)
Lorfast®	Loratadine (10 mg)	Symptomatic treatment of allergic conditions	R38.48 (30 tablets)
Cetlev 5®	Levocetirizine dihydrochloride (5 mg)	Symptomatic treatment of allergic conditions	R66.65 (30 tablets)
Xyzal®	Levocetirizine dihydrochloride (5 mg)	Symptomatic treatment of allergic conditions	R192.16 (30 tablets)
Dazit®	Desloratadine (5 mg)	Symptomatic treatment of allergic conditions	R114.26 (30 tablets)
Desaway®	Desloratadine (5 mg)	Symptomatic treatment of allergic conditions	R123.50 (30 tablets)
Deselex®	Desloratadine (5 mg)	Symptomatic treatment of allergic conditions	R197.19 (30 tablets)
Desodene®	Desloratadine (5 mg)	Symptomatic treatment of allergic conditions	R113.95 (30 tablets)
Neoloridin®	Desloratadine (5 mg)	Symptomatic treatment of allergic conditions	R113.95 (30 tablets)
Pollentyme®	Desloratadine (5 mg)	Symptomatic treatment of allergic conditions	R113.95 (30 tablets)
Fastway®	Fexofenadine HCl (120 mg)	Allergic rhinitis	R35.20 (10 tablets)
Fexaway®	Fexofenadine HCl (120 mg)	Allergic rhinitis	R35.20 (10 tablets)
Fexo®	Fexofenadine HCl 1(20mg	Allergic rhinitis	R37.14 (10 tablets)
Telfast®	Fexofenadine HCl (120 mg)	Allergic rhinitis	R74.44 (10 tablets)
Tellerge®	Fexofenadine HCl (120 mg)	Allergic rhinitis	R34.74 (10 tablets)
Phenergan®	Promethazine HCl (10 mg)	Allergic conditions	R57.77 (100 tablets)
Receptozine®	Promethazine HCl (10 mg)	Allergic conditions	R109.51 (1000 tablets)
Tinset®	Oxatomide (30 mg)	Allergic rhinitis	R243.00 (30 tablets)

HCl: hydrochloride

effects experienced with the intranasal corticosteroids include dryness, stinging, burning and epistaxis. Chronic use of topical corticosteroids may lead to atrophy of the nasal mucosa.[13,18,22] Although the use of corticosteroids constitutes the most effective treatment for the inflammation experienced in allergic rhinitis, when these agents are used for seasonal allergic conjunctivitis, pulse dosing should rather be utilised for as short a treatment duration as possible.[4]

The histamine-1 antihistamines

The H_1-receptor antagonists or H_1 antihistamines include the older-type, sedating, multipotent blockers, or the so-called first-generation H_1 antihistamines, including promethazine, chlorpheniramine, dexchlorpheniramine and cyclizine, and the newer, non-sedating, selective H_1-receptor blockers, or the so-called second-generation H_1 antihistamines. Examples of these non-sedating antihistamines include cetirizine (and levocetirizine), loratadine, ebastine, fexofenadine and mizolastine. The most compelling difference between the two generations of H_1 antihistamines lies in the fact that the first-generation drugs have the ability to cross the blood-brain barrier, while agents belonging to the second-generation have a very limited ability to do so, or none at all. In addition to the aforementioned two generations of systemic (oral and/or parenteral) agents, topical (including intranasal and ophthalmic) H_1antihistamines are available as well.[13,23] Examples of currently available antihistamines are provided in Table III.

First-generation histamine-1 antihistamines

Owing to the fact that these agents have the ability to cross the blood-brain barrier, in addition to being multipotent blocking agents (meaning that they effectively act as receptor blockers in more than one receptor system), their chemical structures allow them some degree of the nonselective, antagonistic effects of an antimuscarinic (or anticholinergic), or an effect that is

Table III: Examples of currently available histamine-1 antihistamines

First-generation histamine-1 antihistamines*	Second-generation histamine-1 antihistamines**
Examples include: • Chlorpheniramine • Cyclizine (syn. meclizine) • Cyproheptadine (used as an appetite stimulant because of to its distinct antiserotonergic activity) • Hydroxyzine • Mepyramine • Oxatomide • Promethazine, a phenothiazine • Trimeprazine (syn. alimemazine), a phenothiazine • Diphenhydramine • Doxylamine • Triprolidine	Examples include: • Cetirizine • Desloratadine • Ebastine • Fexofenadine • Levocetirizine • Loratadine • Mizolastine

*: These are the so-called sedating antihistamines. They cross the blood-brain barrier and act as multipotent receptor blockers. They cause drowsiness, somnolence and impairment of motor function. Drivers, pilots and operators of heavy machinery should avoid using these agents

**: These agents do not cross the blood-brain barrier to any significant degree and do not produce any anticholinergic side-effects.They are non-sedating antihistamines

antihistaminergic, α_1-adrenergic blocking, anti-serotonergic and local anaesthetic in nature.

Other examples include the tricyclic antidepressants and the phenothiazines. Because of the multipotency of their receptor-blocking capabilities, the first-generation H_1 antihistamines have a variety of indications and uses ranging from allergies and rhinoconjunctivitis, to nausea and vomiting, motion sickness and insomnia. However, their anticholinergic side-effects limit their usefulness in a variety of settings, including patients with glaucoma, benign prostatic hyperplasia and in cardiac patients, such as those suffering from ischaemic heart disease, myocardial infarction and congestive heart failure.

Of the wide variety of agents belonging to this group, the following examples are particularly noteworthy:[1,2,3,22]

- *Sedation:* Options include hydroxyzine, promethazine and diphenhydramine. However, more suitable agents can be used to manage insomnia
- *Antiemetic agents:* Examples include cyclizine (syn. meclizine), diphenhydramine, hydroxyzine or promethazine. First-generation H_1 antihistamines may be very useful in the management of postoperative nausea and vomiting, as well as vertigo
- *Allergic reactions:* Chlorpheniramine displays lower levels of sedation than that with many of the other examples in this group, and may therefore be better suited to the management of allergic reactions.

It should be noted that these older-type drugs have never been optimally investigated and profiled from a clinical pharmacology perspective.[23]

Second-generation histamine-1 antihistamines

In addition to not being able to penetrate the CNS to any significant degree, the second-generation H_1 antihistamines are also devoid of any antiemetic activity or anticholinergic side-effects. Of the various agents belonging to this group (including a few examples of the active enantiomers of racemic drugs), the following examples are of particular interest:[1-3,23]

- Fexofenadine has the shortest half-life of the systemic agents. Therefore, it should be taken twice daily. (The others only require once-daily dosing intervals). Also, it does not display any H_1-receptor occupancy inside the CNS at therapeutic dosages (Figure 2)
- Cetirizine has the greatest likelihood of displaying some degree of H_1-receptor occupancy inside the CNS, which may result in some level of sedation, albeit in higher-than-recommended dosages
- The first two examples of the so-called second-generation H_1 antihistamines, namely terfenadine and astemizole, were withdrawn from the market because of unacceptable levels of cardiac toxicity.

Note that the H_1 antihistamines do not form the mainstay of treatment in cases of severe angioedema or anaphylaxis, but may be used as effective adjunctive therapy to adrenaline and other emergency drugs and resuscitative interventions in such instances.[1-3]

Ophthalmic (eyedrop) preparations include levocabastine, epinastine, olopatadine and ketotifen. (The latter also acts as a mast cell stabiliser). Levocabastine, in addition to azelastine, is also available as a nasal spray for use in patients with allergic rhinitis.

Conclusion

Currently, the second-generation H_1 antihistamines are widely considered to be the mainstay of treatment for allergic disease, especially since they have been found to be largely devoid of the cumbersome side-effects and resultant contraindications of the older-type, first-generation H_1 antihistamines. The latter drugs are no longer favoured in this setting, but are still being widely used for a number of other diverse indications. In addition to systemic treatment, the topical application of second-generation H_1 antihistamines, as well as that of the decongestants and corticosteroids, is also used successfully in the management of allergic rhinoconjunctivitis. The H_1 antihistamines are a diverse and very useful class of pharmacotherapeutic agents with high application value in the clinical practice setting.

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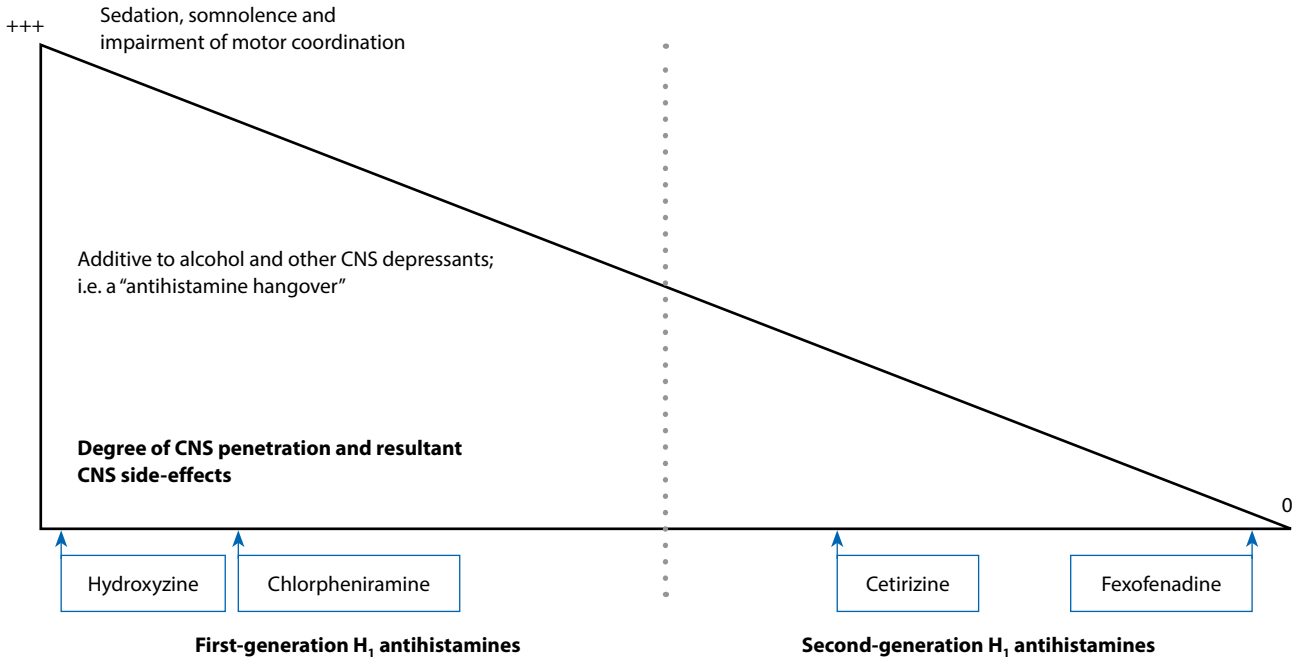

CNS: central nervous system, H_1: histamine 1, +++: represents maximal central nervous system side-effects, 0: represents an absence of central nervous system side-effects

Figure 2: An approximation of the degree of central nervous system penetration and the resultant central nervous system side-effects of the first-generation histamine-1 antihistamines versus the second-generation histamine-1 antihistamines

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