Antihistamines: a brief review

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Introduction

The prevalence rates of allergic diseases such as allergic rhinitis and asthma appear to be increasing in many countries. Although several mediators are involved in the pathophysiology of allergic diseases, histamine plays a fundamental role, particularly in allergic rhinitis and urticaria. Produced and stored within the cytoplasmic granules of mast cells and basophils, histamine is released in large quantities during the immediate phase of allergic reactions.

Histamine exerts its effects in allergic diseases primarily by interacting with H_1 receptors present in a variety of organs. In the nose, histamine stimulates the sensory nerve endings (causing itching and sneezing), and increases vascular permeability (causing oedema and obstruction) and glandular secretions (causing rhinorrhoea). In the skin, histamine provokes vasodilation and increases vascular permeability (causing erythema and oedema) and stimulates sensory nerve endings (causing itching). In chronic allergic inflammation, histamine has effects on inflammatory cells and causes cellular activation (mast cells, basophils and eosinophils) and the release of proinflammatory mediators such as leukotrienes and cytokines

Antihistamines are most often used to provide symptomatic relief of allergic symptoms caused by histamine release. Antihistamines have remained at the forefront of treatment for allergic diseases for many years and are among the most commonly prescribed medicines in children. However, the use of any medication in this age group requires careful consideration of safety criteria. The recent requirement of the Medicines Control Council in South Africa to contraindicate the use of promethazine in children under the age of two years underlines the emphasis on medicine safety in this patient population. Furthermore, a Cochrane Review concluded that the efficacy of antihistamines when used for chronic nonspecific cough in children is uncertain and that antihistamines should not be recommended as empiric therapy for children with chronic cough.

The safety and appropriate use of antihistamines is clearly still debated, warranting a brief review of their therapeutic uses and safety issues.

Antihistamines and the generation gap

Antihistamines comprise a broad class of pharmacological agents that include the first-generation, relatively sedating H_1antagonists (e.g. diphenhydramine) and the newer, second-generation, less- or nonsedating H_1 antagonists (e.g. loratadine).

Depending on their effects on the central nervous system (CNS), antihistamines are divided into "classic" or first-generation antihistamines and newer, second-generation antihistamines. Although the second-generation antihistamines were designed to overcome the sedative effects associated with the first-generation agents, several of the second-generation agents are not free from sedative effects at higher doses. It is important to emphasise that sedation is not just sleepiness, but also refers to cognitive impairment that may be detrimental to daytime activities, including school and work performance, driving ability and other tasks that require a high degree of concentration and alertness.

Other histamine-receptor antagonists, such as cimetidine or ranitidine, work primarily on H_2 receptors, causing inhibition of gastric acid secretion, while still other experimental antihistamines act on presynaptic H_3 receptors. The term "antihistamine" is normally reserved for histamine-1 receptor antagonists.

Over the last 20 years, new H_1-antihistaminergic compounds have been synthesised, with different pharmacokinetics and pharmacodynamics. Several of these new compounds also exhibit antiallergic and anti-inflammatory properties that are independent of their action on the H_1 receptor.

Other developments, generally in the form of active metabolites or enantiomers, led to the use of the term "third-generation" antihistamines. This term emerged

spontaneously, with no clear definition of its meaning or clinical implications. For example, some authors identified third-generation antihistamines as those being free from CNS effects, while others defined third-generation antihistamines as those being free from cardiotoxic potential, and for still others, third-generation antihistamines are those free from CNS effects and cardiotoxic potential. Antihistamines with antiallergic and anti-inflammatory effects have also been as assigned to the "third generation".

However, the Consensus Group on New Generation Antihistamines has concluded that, "to merit a new class of antihistamines, the antihistamine under evaluation would have to demonstrate distinct clinical advantages over existing compounds and fulfil at least three prerequisites: freedom from cardiotoxicity, drug interactions and effects on the CNS." On the basis of the evidence available, the Consensus Group considered it premature to reclassify H_1 antihistamines and to recognise any currently available H_1 antihistamine as "third generation".

Although the efficacy of the H_1 antihistamines in the treatment of allergic diseases is similar, even when comparing first- and second-generation agents, H_1 antihistamines are markedly different in terms of chemical structure, pharmacology and toxic potential. Second-generation antihistamines are, in general, better tolerated when compared with their predecessors. However, some adverse effects, e.g. cardiotoxicity, have been reported with some of them, notably terfenadine and astemizole.

Knowledge of the pharmacodynamics (i.e. drug-receptor interactions) and the pharmacokinetics (i.e. absorption, distribution, metabolism and excretion) is important for the appropriate use of these medicines, particularly in vulnerable or high-risk patient populations such as children and the elderly.

Pharmacodynamics

The requirements for the approval of a new medication have led to the availability of much more information on the pharmacokinetics and pharmacodynamics of the second-generation antihistamines when compared with the information available on the first-generation agents. This consideration alone would advise the more widespread use of the second-generation antihistamines.

Four types of histamine receptors have been identified: H_1, H_2, H_3 and H_4. All H_1 antihistamines are reversible, competitive inhibitors of H_1 receptors.

First-generation H_1 antihistamines act both on peripheral and central H_1 receptors. They are also potent competitive inhibitors of muscarinic receptors and have significant anticholinergic effects (e.g. drying of nasal secretions) and anticholinergic side-effects (e.g. dry mouth, urinary retention, blurred vision, sinus tachycardia). The phenothiazine class of H_1 antihistamines (e.g. promethazine) has α-adrenergic blocking activity, which may cause hypotension.

Second-generation H_1 antagonists have high affinity and selectivity for the peripheral H_1 receptor. They have a lower binding affinity for the cholinergic (muscarinic) and α-adrenergic receptor sites than the first-generation antihistamines. Antimuscarinic effects have not been reported with most of the second-generation antihistamines. However, desloratadine, does appear to interact with the five subtypes of muscarinic receptors but despite its potential to interact with these receptors, no significant anticholinergic effects have been reported. Specificity for the peripheral H_1-receptor site avoids the potential for adverse effects on the CNS.

In addition to acting on H_1 receptors, many second-generation H_1-receptor antagonists are capable of inhibiting not only the release of histamine by mast cells, but also mast cell activation itself. Some are able to regulate the expression and release of cytokines, chemokines and inflammatory mediators. These properties are referred to as the antiallergic and anti-inflammatory effects of the antihistamine and are not related to the direct effects on the H_1 receptor. Since nasal obstruction is a prominent component of chronic allergic inflammation or the late allergic response, the second-generation antihistamines may lessen symptoms of nasal obstruction, an effect not seen with the first-generation drugs. Nonetheless, for an H_1 antihistamine to have truly significant antiallergic or anti-inflammatory properties, it must show similar or superior efficacy to existing therapies, e.g. the corticosteroids.

There are six structural classes of antihistamines (Table I). Although characteristic pharmacological properties have been described for each structural class, it should be noted that many of the effects of the antihistamines vary from patient to patient. A specific antihistamine that provides dramatic relief without adverse effects in one patient may produce intolerable adverse effects in another patient.

Pharmacokinetics

When selecting an antihistamine for a particular patient, the pharmacokinetics of the various antihistamines needs to be considered (Table II).

Most antihistamines show good absorption when administered orally, as is demonstrated by the fact that effective plasma concentrations are usually reached within three hours of dosing. Most antihistamines are metabolised in the liver by the group of enzymes belonging to the cytochrome P450 (CYP) enzyme system, i.e. CYP2D6 or CYP3A4. Metabolic breakdown products of antihistamines are then eliminated through the kidneys. Only acrivastine, cetirizine, levocetirizine, desloratadine

Table I: Structural classes of H_1 antihistamines

Alkylamines (propylamines)	Ethanolamines	Ethylenediamines	Phenothiazines	Piperidine	Piperazines
First generation					
Brompheniramine Chlorpheniramine Dexchlorpheniramine Pheniramine Triprolidine	Clemastine Diphenhydramine Doxylamine	Antazoline Mepyramine	Promethazine Trimeprazine	Azatadine Cyproheptadine	Buclizine Cyclizine Hydroxyzine Mebhydrolin Meclizine
Second generation					
Acrivastine				Astemizole Desloratadine Ebastine Fexofenadine Levocabastine Loratadine Mizolastine Terfenadine	Cetirizine Levocetirizine

Olopatadine and azelastine differ structurally from other available antihistamines

Table II: Pharmacology of the currently available H_1 antihistamines used in allergic disease

Antihistamine	Onset of effect	Metabolism in liver	Drug interactions	Elimination half-life	Dosage
First generation					
Chlorpheniramine	30 minutes SR: 2 hours	Yes (CYP2D6)	Alcohol, CNS depressants, tricyclic antidepressants, anticholinergics, medicines affecting CYP2D6 enzymes	20 hours	SR: 8 mg every 12 hours or 4 mg every 6 to 8 hours
Clemastine	2 hours	No (conjugation)		10-12 hours	1 mg twice daily
Diphenhydramine	2 hours	Yes (CYP2D6)		7-11 hours	25-50 mg every 8 hours
Hydroxyzine	2 hours	Yes		16-24 hours	25-50 mg every 8 hours
Promethazine	30 minutes	Yes (s-oxidation)		4-8 hours	25 mg at night
Second generation					
			Medicines metabolised by same route, e.g. ketoconazole and erythromycin by CYP3A4 enzymes		
Acrivastine	1 hour	Yes (< 50%)	Improbable	1.4-3.1 hours	8 mg every 8 hours
Cetirizine	1-3 hours	Yes (< 40%)	Improbable	7-11 hours	10 mg once daily
Desloratadine	2 hours	Yes (3A4;2D6)	Improbable	27 hours	5 mg once daily
Ebastine	2 hours	Yes (3A4)	Possible	10.3 ± 19.3 hours	10-20 mg once daily
Fexofenadine	2 hours	Minimal (< 8%)	Improbable	14 hours	120-180 mg once daily
Levocetirizine		Minimal (< 15%)	Improbable	8 hours	5 mg once daily
Loratadine	1-3 hours	Yes (3A4; 2D6)	Improbable	12-15 hours	10 mg once daily
Mizolastine	1 hour	Yes (glucuronidation and minor 3A4 and 2D6)	Possible	12.9 hours	10 mg once daily

SR: slow release

and fexofenadine avoid this metabolic passage through the liver to an important degree. Cetirizine and levocetirizine are eliminated in urine, mainly in unaltered form, while fexofenadine is eliminated in stools following excretion by the biliary tract, without metabolic changes.

Therapy

Allergic rhinitis

Antihistamines are most beneficial in the management of nasal allergies. In patients with allergic rhinitis, H_1 antihistamines ameliorate itching, sneezing and watery rhinorrhoea, symptoms characteristic of the early allergic response to antigen. Most antihistamines are not as useful for controlling nasal obstruction, a result of the late phase of the allergic reaction. However, more recent clinical trials with some second-generation antihistamines with antiallergic and anti-inflammatory effects, such as desloratadine, fexofenadine and levocetirizine, have shown improved nasal symptoms, including obstruction in patients with allergic rhinitis.

First-generation antihistamines are no longer recommended for the treatment of allergic rhinitis. Only the second-generation, nonsedating antihistamines should be used for chronic management of this condition. Evidence shows that continual use in allergic diseases is more effective than use on an "as required" base. Long-term use may even improve lower airway symptoms in patients with allergic rhinitis and asthma. Some antihistamines, e.g. azelastine, may also be administered intranasally for the short-term management of seasonal allergic rhinitis.

Allergic conjunctivitis

When administered orally, antihistamines exert their effect not only on nasal symptoms, but also on ocular symptoms, which are frequently associated with allergic rhinitis. Although oral antihistamines may be effective, symptoms of allergic conjunctivitis are often best managed with an ophthalmic preparation.

Atopic dermatitis and urticaria

Antihistamines are often effective in the treatment of allergic dermatoses. Atopic dermatitis is a common inflammatory skin condition that usually affects children. Emollients are the mainstay of maintenance therapy for atopic dermatitis, while topical corticosteroids are first-line treatments for acute flare-ups. Sedating antihistamines administered at night are useful for the treatment of atopic dermatitis when patients have sleep disturbances and concomitant allergic conditions.

In patients with chronic urticaria, antihistamines relieve itching and reduce the number, size and duration of urticarial lesions.

Motion sickness and vertigo

Some antihistamines, such as diphenhydramine, cyclizine, meclizine and promethazine, are useful for the prevention of the nausea, vomiting and vertigo associated with motion sickness.

Insomnia

Some antihistamines, especially the ethanolamines such as diphenhydramine and doxylamine, are used for their sedative effects as night-time sleep aids in individuals who experience occasional sleeplessness or who have difficulty falling asleep.

Colds and coughs

Although first-generation antihistamines are frequently used for the symptomatic treatment of the common cold, evidence of effectiveness remains to be clearly established. While first-generation antihistamines with anticholinergic activity are considered effective in reducing rhinorrhoea and sneezing associated with the common cold, they may cause thickening of mucus secretions, making them more difficult to cough up.

The routine administration of fixed combinations of antihistamines, decongestants, caffeine, analgesics and anticholinergics has been questioned. Single-ingredient products are safer than combination products and also facilitate dosage adjustment. There is no evidence that combinations containing two or more antihistamines are more effective than one antihistamine or that combinations of subtherapeutic doses of two or more antihistamines are more effective than one antihistamine in therapeutic dose. Nonetheless, some combination products offer a convenient approach to the management of symptoms associated with colds and flu, provided that the ingredients are provided in therapeutic doses, that they do not have opposing effects and that they relieve the patient's presenting symptoms.

Some first-generation antihistamines, such as diphenhydramine, have been used effectively as antitussives for patients with a dry, irritating cough. However, it is important to bear in mind that cough suppressants, including antihistaminergic agents, should not be used in patients with a productive cough, characterised by the presence of sputum. Cough remedies that contain an antihistamine and an expectorant are also not considered therapeutically sound, as these two medicines have opposing therapeutic effects.

Drug interactions

Since H_1 antihistamines are often prescribed for prolonged periods, the possibility that they may interact with other medicines should always be taken into consideration.

The first-generation antihistamines are lipid soluble and penetrate the CNS. They therefore have the potential to add to the sedative effects of other medicines, including alcohol.

Drug interactions may also occur when administering H_1 antihistamines with CYP liver enzyme inducers or inhibitors. For example, the concentration of the antihistamine may increase when it is administered together with other medicines that inhibit the CYP system. In these cases, the safety margin of the antihistamine, i.e. the concentration range for which the incidence of adverse effects is minimal, will be an important consideration, since the plasma levels may be unpredictable.

Most first-generation antihistamines are themselves inhibitors of the CYP2D6 hepatic enzymes. They may therefore alter the metabolism of other medicines dependent upon CYP2D6 metabolism, such as venlafaxine, tricyclic antidepressants, some antipsychotics, β blockers, antiarrhythmics and tramadol.

All second-generation antihistamines, with the exception of cetirizine, levocetirizine and fexofenadine, are metabolised by the CYP3A4 enzyme system in the liver. Therefore, the concurrent use of other medicines (e.g. the macrolides, antifungals or calcium-channel blockers) metabolised by CYP3A4 increases the potential for drug interactions with these antihistamines. Nonetheless, concomitant use of these medicines generally does not lead to serious side-effects, primarily because of the wide safety margin of the second-generation antihistamines.

Side-effects

Central nervous system

H_1 receptors are widely distributed throughout the CNS and the first-generation H_1 antagonists may cause several effects on the CNS such as sedation, problems with coordination, dizziness, lack of concentration and, paradoxically, agitation and excitability, particularly in children and in the elderly.

An important determinant of the potential for CNS adverse effects is the capacity of the compound to cross the blood-brain barrier (BBB). Crossing the BBB depends on the chemical properties of the compound such as lipophilicity and molecular weight. First-generation antihistamines are highly lipid soluble and have a low molecular weight and a high affinity for cerebral H_1 receptors, which means that CNS side-effects such as sedation occur frequently, even at therapeutic doses. Second-generation antihistamines, in contrast, have greater molecular weight, low lipid solubility and low affinity for cerebral H_1 receptors. Therefore, most second-generation antihistamines at therapeutic doses are devoid of significant side-effects on the CNS.

Cardiac effects

Adverse cardiac effects (torsades de pointes, arrhythmia and prolongation of the QT interval) have been reported with two second-generation agents, astemizole and terfenadine. These cardiotoxic effects appear to be dose related and have invariably been reported when these compounds were used at doses above the recommended levels or in association with other medicines metabolised by the same hepatic enzyme system. It is important to point out that these cardiac adverse effects are not class related, as they are not related to the blockade of the H_1 receptor and appear to be limited to terfenadine and astemizole. Other second-generation antihistamines, such as cetirizine, fexofenadine and levocetirizine, which are minimally metabolised, are safer alternatives.

Paediatric precautions

Children are more susceptible than adults to the adverse effects of antihistamines. Children are also at increased risk for experiencing paradoxical CNS stimulant effects with the antihistamines. Promethazine has been contraindicated for use in children under the age of two years and should be used with caution in children over the age of two years.

The first-generation antihistamines have never been adequately studied in paediatric age groups. In contrast, the second-generation antihistamines have been subjected to several studies in children, which have provided a better knowledge of their safety profiles and appropriate paediatric doses.

Conclusion

There are important differences in the chemical structures, pharmacodynamics, pharmacokinetics and adverse events of antihistamines. As a result, detailed knowledge of these differences is recquired when recommending one antihistamine over another for the treatment of allergic disorders, particularly when the patient belongs to a high-risk group, i.e. children, the elderly, those with underlying disease conditions and those taking other medicines concurrently.

In conclusion, the noncardiotoxic, second-generation antihistamines are usually the medicines of choice for patients of all ages in the management of allergic disorders, while the first-generation antihistamines should be held in reserve for the infrequent situations where their adverse effects, e.g. sedation, may be desirable.

Bibliography available on request