Old and New Antihistamines

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Histamines is a bioactive compound that have been identified in several organs and tissues in practically animal series, including man. The physiological role of histamine is not clearly defined. In contrast, a very large number of experimental and clinical data indicate that histamine partly responsible for the clinical aspect of several diseases. In 1910, Dale and Laidlaw[1] showed that the phamacological effects of histamine were comparable to the symptoms described with manifestations of immediate hypersensitivity Histamine is stored in the mast cells.[2] These cells are present in the perivascular space of several organs, and are present in great quantity in the nasal and ocular mucous membranes, in the bronchial and pulmonary tissue, and in the skin. It is acknowledged the the degranulation of mast cells associated with release of histamine is a fundamental mechanism responsible for the clinical allergic conditions.[3] According to the localization of the phenomenon, various allergic manifestations are observed; they are mainly present at two level: the respiratory level (rhinitis and asthma) and the cutaneous level (urticaria). Inhbition of the activity of histamine in these various diseas will produce a definite therapeutic effect.

The first antihistaminic substances were synthesized between 1937 and 1944.[4-6] The clinical use of antihistamines was generalized after World War II.[7] Their use and clinical efficacy are limited by pharmacological properties other than their antihistaminic actitivity. These additional effects include : an anticholinergic activity, a local anaethetic activity, and a depressant activity at the level of the central nervous sytem (CNS). Conventional antihistamines do not inhibit some of the pharmacological effects of histamine. Ash and Schild[8] were the first to put forward the concept of two different receptors for histamine. Black et al[9] confirmed the existence of a second recptor (H_2) for histamine, responsible for the effect of histamine on gastric secretion. Since then specific anti-H_2 substances have been developed and are used mainly for the treatment of peptic diseases. A recently described H_3receptor is thought, to be implicated in histamine's regulation of its own synthesis and release from central and peripheral nerve tissue.[10, 11]

In recent years, H_1 antihistamine have been developed that have little or no CNS depressant effect. This class of drugs are the non-sedating H_1 antagonists. Their lack of the sedating properties that are so characteristic of earlier H_1 blockers has been ascribed to their very limited ability to cross the blood-brain barrier.

H_1 Antihistamines

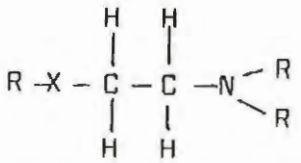
Chemistry and Pharmacology

Histamine is a physiologically active, endogenous substances that binds to and activated H_1 and H_2 receptors on various cells. This binding causes microvascular dilation, increased vascular permeability, smooth muscle stimulation, and nerve ending stimulation, which result in itching.

The term antihistamine has historically been used to describe medications that act as H_1 receptor antagonists. They appear to act by blocking H1 receptor sites, thereby preventing the action of histamine on the cell; they do not chemically inactivate or physiologically antagonize histamine nor do they usually prevent the release of histamine; exceptions include ketotifen,[12] azatadine,[13] azelastine.[14, 15]

The basic ethylamine group is common to most antihistamine and also to anticholinergic and local anesthetic agents. The antiemetic and antimotion sickness actions of some antihistamines appear to results, in part, from their central anticholinergic and CNS depressant properties. The antipruritic effect results from a peripheral antihistaminic effect and possibly a local anesthetic effect, the sedative effect of antihistamines may also contribute to their antipruritic activity.

In general, antihistamines can be depicted by the following formular:



Presumably the core ethylamine (CH_2 CH_2 N) competes with histamine for cell receptors, whereas the substitutions modify the absorption, excretion, or side effects. Antihistamines can be classified on the basis of X substitution into seven classes (Table 1)

Antihistamines are well absorbed after oral administration. Symptomatic relief of allergic reactions usually begins within 30 minutes and is substantial within 1 hour. The duration of action is variable, but symptoms are usually relieved for at least 4 to 6 hours, due in part to the relatively long serum elimination half-life values.[16, 17] However, maximal antihistaminic effects of the drugs do not correlate with peak serum concentrations and persist as serum concentrations are declining. There may be some decrease in effectiveness with prolonged use of these agents,[18] but a substantial degree of tolerance to the antihistaminic effects does not generally occur. Nonetheless, tolerance to the sedative effects may develop.[19] The anticholinergic and sedative effects are due to the lipid solubility of many of the classical compounds which allow them to cross the blood-brain barrier and interact with the H_1 receptors of the CNS. The newer nonsedating antihistamines, ofter analogues or even active metabolites of the classical agents, have a molecular structure that interferes with passage into the brain. The metabolic fate of most antihistamines appear to be chiefly in the liver, with excretion as inactives metabolites within 24 hours in urine.

Uses

Antihistamines are benefical in the management of allergic rhinitis-both, seasonal and perennial, allergic conjuntivitis and allergic skin diseases such as urticaria and atopic dermatitis. Symptomatic relief of nasal itching, sneezing, rhinorrhea, ocular itch, skin itching, erythema, lacrimination, dermal swelling is usually provided by antihistamines. with the alkylamine and the piperazine classes usually the most overall effective.[20] The anticholinergic activity may also be useful in the treatment of rhinitis as it tends to reduce nasal hypersecretion. Chronic nasal congestion and headaches caused by edema of the sinus mucosa are less effected by these agents.[21] 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 therapeutic doses of one antihistamine.[22] Fixed medication combinations of an antihistamine and a nasal decongestant are appropiate if each ingredient has demonstrated clinical efficacy and is present in therapeutic dosage.[23] An additional benefit of the sympathomimetic is that it may counterbalance the sedative properties of the antihistamine. Because antihistamine only block the effect of histamine, for some patients greater relief symptoms awaits the development of medications that can prevent or modify the release of or the effects of the other mediators of the allergic response. Ahithistamines are generally less effective in the treatment of nonallergic rhinitis and vasomotor rhinitis.

Table 1. Antihistamine classes

Chemical class	Generic name	Comments
I. Ethanolamine	Carbinoxamine Clemastine Diphenhydramine Doxylamine	This group of antihistamine has substantial anticholinergic activity. They also commonly cause CNS depression; with usual doses, drowsiness occurs in 50% of patients. Incidence of adverse GI effects is low.
II. Ethylenediamine	Methapyrilline Pyrilamine Tripelenamine	Relatively weak CNS effects; however, drowsiness in some patients. Adverse GI effects are common.
III. Alkylamine	Brompheniramine Chlorpheniramine Dexchlorpheniramine Triprolidine	Cause less drowsiness and some CNS stimulation than others and are thus suitable for daytime use.
IV. Piperazine	Hydroxyzine HCl Hydroxyzine Pamoate	Hydroxyzine is used as a transquilizer, sedative, antipruritic. Anticholinergic effects and drowsiness are common.
V. Phenothiazine	Methdilazine Promethazine Trimeprazine	Used as antipruritic and antiemetic
VI. Piperidine	Azatadine Cyproheptadine	Cyproheptadine causes weight gain and pronounced sedation.
VII. Miscellaneous	Acrivastine Astemizole Azelastine Cetirizine Loratadine Mequitazine Rocastine Temelastine Terfenadine	Most of this group causes significantly less sedation than other classes.

Adverse Effects

Adverse effects vary in incidence and severity with the individual antihistamine and with individual patients. Most mild reactions may be relieved by a reduction in dosage or change to a different class. Some adverse effects disappear with continued therapy CNS depression is common with usual dosage especially with the ethanolamine derivative Sedation can range from mild drowsiness to deep sleep. Dizziness and disturbed coordination may also occur. Individual who perform potentially hazardous task requiring mental alertness or physical coordination (for example, operating machinery, driving a motor vehicle) should be warned. Patients should also avoid consuming alcoholic beverage while taking antihistamines as they may potentiate the CNS effects. The new nonsedating antihistamines have significantly contibuted to the solution of this problem. Some patients especially children, experience paradoxic CNS excitement characterized by restlessness and insomnia with antihistamine therapy.

Table 2. Formulations and dosages of some representative H_1-antihistamines

Generic (proprietary)	Formulation	Recommended dose
Alkylamine		
Chlorpheniramine	Syrup, 2.5 mg/5 ml; tab. 4 mg; time-release, 8, 12 mg; parenteral solution, 10 or 100 mg/ml	Pediatric, 0.35 g/kg/24 hrs; Adult, 8-12 mg bid.
Brompheniramine maleate	Syrup, 2 mg/5 ml; tab. 4 mg time-release, 8, 12 mg	Pediatric, 0.35 mg/kg/24 hrs. Adult, 8-12 mg bid.
Ethanolamine		
Diphenhydramine HCl.	Elixir, 12.5 mg/5 ml; Capsule 25 or 50 mg; parenteral solution, 10 or 50 mg/ml	Pediatric, 2.5 mg/kg/24 hes. Adult 25-50 mg tid.
Piperazine		
Hydrxyzine HCl.	Syrup, 10 mg/5 ml Capsule, 10, 25, 50 mg	Pediatric, 2 mg/kg/24 hrs. Adult, 25-50 mg, bid.
Piperidine		
Cyproheptadine HCl	Syrup, 2 mg/5 ml; tab. 4 mg	Pediatric 0.25 mg/kg/24 hrs. Adult 4-8 mg tid.
Azatadine maleate	Tab. 1 mg	Pediatrix, 0.5-1 mg bid. Adult, 1 mg bid.
Other		
Terfenadine	Suspension, 30 mg/5 ml; Tab. 60-120 mg	Pediatric, 3-6 yr. 15 mg bid, 7-12 yr, 30 mg bid. Adult, 60 mg bid. or 120 mg OD.
Astemizole	Suspension, 10 mg/5 ml; Tab. 10 mg	Peadiatric, 0.2 mg/kg/24 hrs. Adult, 10 mg OD.
Loratadine	Tab. 10 mg	Adult, 10 mg OD.

Adverse GI effects of antihistamines include anorexia, epigastric distress, nausea, diarrhea, or constipation. Adverse anticholinergic effects include dryness of the mouth, nose and throat; urinary retention; impotence; visual disturbances; blurred vision; and nervousness and irritability. Drying of secretions sufficient to aggravate asthma is not a clinical problem; the potential benefits of antihistamine treatment of allergic rhinitis should not be denied to a patient who also has asthma.[24]

Dosage

Recognition of the prolonged duration of the biologic effects has led to improves regimens of antihistamine administration. Dosing once daily at bedtime or twice daily, with the bulk of the recommended daily dose at bedtime, can often achieve symptom control without daytime sedation. Chemical efficacy of antihistamines is notably greatest when they are given before the allergen exposure. Short-acting preparations are useful for this purpose or for intermittent symptoms. Longeracting prepararions are indicated for chronic conditions when they are regulary sporadically. There are some forms of the short-acting antihistamine are modified to be the form of longer-action such as repeat tab or chronotab of chlorpheniramine and brompheniramine. Usually the lack of response to an antihistamine is due to the severity of the disorder or a secondary complication (for example, infection or polyp). However, tachyphylaxis can occur by hepatic enzyme induction. Although this is infrequent, it can be altered by either changing to a different antihistamine class or, becuase of cross-tolerance to chemically unrelated antihistamines,[25] by switching to a different therapeutic modality.

Among the **new (or second geration) antihistamines**, terfenadine and astemizole deserve special attention. They are almost exclusely H_1 antagonists. They fail to penetrate the CNS and, most importantly, cause no sedative or anticholinergic effects.

Terfenadine is rapidly absorbed with a peak plasma concentration at 2 hours after an oral dose. It is metabolized by the liver and excreted in the usine and feces. The elimination half-life is between 16 and 23 hours.[26] It has been available as 60-mg tablet to be administered twice a day. Acitivity is seen in most patients after a single dose, but maximum response may not occur for 3 days.[27] An oral suspension for children and a pseudoephidrine combination are currently being investigated. Terfenadine does not impair psychomotor performance,[28] adversely affect subjective feeling, or potentiate the effect of alcohol. However, it is much more expensive than the older H_1 antihistamines.

Astemizole is presently available. It is also rapidly absorbed and distributed with a peak plasma level occuring about 1 hour after a dose. Because of its strong affinity for H_1 receptor, it is quite slowly eliminated half-life of 104 hours. Astemizole has a prolonged action consistent with its slow elimination.[29] Dermal response to histamine are modified for 12 hours with terfenadine, for several days with astemizole after single oral dose and for months after multi dosing with astemizole. The current recommended dose of astemizole for adults is 10 mg once a day, for children 6 to 12 years ½ tab. (5 mg) or 1 tsp of suspension preparation once a day, and children under 6 years old 0.2 mg/kg body wt/day. The once-a-day regime should aid compliance, and the long duration of action should maintain protection if a dose is missed. Astemizole has been documented to be effective in the treatment of seasonal allergic rhinoconjuncitivits[30, 31] and perennial allergic rhinitis.[32] As with other antihistamines, it is effective more for the "sneezer" and "blower" than for the "blocker". Because of its slow onset of its activity, it is sometimes helpful to give a loading dose for the initial 1 to 3 days of therapy. Increased appetite and wight gain have been noted in some patients receiving astemizole.[31, 32] The medication on the developing fetus is a potential risk that lasts at least 8 weeks after the last dosing. Therefore, women of childbearing potential should not use astemizole unless they take adequate contraceptive precautions.

Mequitazine is a phenothiazine derivative antihistamine of the new generation, which has a anti H_1 type antihitamine and inhibits mast cell degranulation. It has 2 specific advantages, a long duration of action and absence of effects on alertness.[33] If taking by mouth, the peak of blood level during the first hour. The side effects of this drug may be fleeting episodes of dry moth and constipation. The usual dosage in adult is 2 tabs/day, 1 in the morning and 1 at night. One tablet contains of 5 mg. of the drug. The solution preparation is not available.

Clemastine fumarate belongs to the benzhadryl ether group of antihistamine compound. It is an antihistamine with anticholinergic (drying) and sedative side effects This drug appears to compete with histamine for cell recptor sites on effector cells.[34] Clemastine demonstrates that it is rapidly and nearly completely absorbed from the GI-tract when taking by mouth and peak plasma concentrations are attained in 2-4 hours, and urinary excretion is the major mode of elimination. In normal human subjects who received clemastine injections over 24 hour period, the drug persists for 10-12 hours and in some case, for as long as 24 hours. Transient drowsiness is the most common side effect of clemastine. Recommended does for adult is starting with a one tablet (1.34 mg) three times daily. Dosage may be increased as required, but not to exceed six tablets daily. For children under 6 years old 1-5 cc.of syrup (5 mg/5 ml.) can be given before breakfast and at bed time.

Azatadine maleate is antihistamine, related to cyprohepatadine, with antiserotonin, anticholinergic (drying) and sedative effects.[35] The drug when taken by mouth will be readily absorbed with peak plasma levels at about 4 hours after dosing. Approximate 50% is excreted in the urine. Because of its drying effect, it should be used with cautions in asthmatics. It will increse the ocuular pressure, therfore it should not be used in patients with narrow angle glaucoma. Use of this drug during pregnancy or lactation is not recommended.[35] The recommended dosage for adult is 1 tablet (1 mg) in the morning and evening, for children under 6 years of age is ½ tsf of syrup (0.5 mg/5 ml.) twice daily.

Oxatomide is a diphenylmethyl piperazine derivative, chemically related to antiasthmatic agent cinnarizine. It has been shown to be a potent blocker of H_1-receptor and also a potent anti-anaphylactic agent that inhibits the release of histamine and probably also of other mediators of anaphylaxis.[36, 37] Oxatomide is well absorbed in man after oral administration, peak plasma level occur 3 hours after an oral dose and plasma level declines with an elimination half-life of 14 hours. Recommended adult dose is 1 tablet (30 mg) after breakfast and supper, the children is about 0.5 mg/kg per intake. This drug is available in teablet form. Somnolence is rare with the recommended doses and is usually transient in nature. If required the dose can be temporarily reduced. An increases of appetite has been observed with high doses.

Loratadine is a potent, long acting antihistamine which is relatively specific for peripheral histamine H_1-receptors, penetrates poorly into the CNS and thus lack of depressant effects. Structually the drug is related to azatadine, with a neutral carbamate group replacing azatadine's basic tertiary amino group and a chloro group added to the benzocycloheptapyridine ring systam.[38] Loratadine binds selectively to peripheral histamine H_1-receptors, displaying little or no affinity for CNS receptors. Loratadine possesses only weak affinity for alpha-adrenoceptors or acetylcholine receptors. This drug also has antiserotonin activity, it is a more potent inhibitor of serotonin-induced bronchospasm in guinea-pigs than is terfenadine.[39] Loratadine also has antiallergic activity by inhibiting antigen-induced bronchospasm.[39] The recommended adult dosage of loratadine is 10 mg (1 tablet) once daily. No pediatric dosage instructions are currently available, although results from clinical trials indicate that for children ages 6 to 12 years a dosage of 5 to 10 mg once daily is appropiate.

Cetirizine, a carboxalated metabolite of hydroxyzine, possesses the parent compound's antihistamine activity but does not cause sedation. This lack of CNS effects may be due to cetirizine's greater selectivity or potent at H_1 receptors in peripheral tissues, or it may result from the agents's relative exclusion from the CNS compartment.[40] This drug also inhibits the increase in nasal airway resistance after an allergen challenge and reduces bronchoconstriction after histamine inhalation.[41] Cetirizine is inactive against serotonin or acetylcholine-mediated smooth muscle contraction.[42] When taking by mouth, the peak mean concentration is achieved within 1 hour. Mean concentration of cetirizine declines biexponentially and has a mean elimination half-life of 7.4 hours. The drug is excreted quite repidly, with 60% of the dose recovered in the 24-hour urine.[43] Recommended adult dose is 5 to 20 mg/day. Pediatirc solution is not available at present. Cetirizine is not available in Thailand.

H2 Antihistamines. Histamine acts on the vascular tree to cause vasodilatation. This involves both H_1 and H_2 receptors distributed throughout the resistance vessels. H_1 receptors have a higher affinity for histamine and mediate a dilator response that is relatively rapid in onset and short lived. By contrast, activation of H_2 receptors cause a dilation

that develops more slowly and is more sustained. The effects of large doses of histamine are completely blocked only by a combination of H_1 and H_2 receptos antagonists.

Cimetidine and ranitidine are H_2 receptor antagonists. Cimetidine and ranitidine have been primarily evaluated as inhibitors of the action of histamine to reduce gastric acid output. However, there is evidence that a combination of H_1 and H_2 antagonist are more effective than either one alone in suppressing immediate and late IgE-mediated cutaneous hypersensitivity reactions[44] such as chronic urticaria,[45] and nasal congestion from histamine nasal challenge.[46] Although H_1 histamine receptor anatagonists are effective in the treatment of allergic rhinitis, they often produce only partial relief. A clinical evaluation of the additive effect of the H_2 antagonist, cimetidine, to the H_1 antagonist, chlorpheniramine, significantly reduced allergic symptoms and the need for supplemental medication.[47] Cimetidine, because of its cost and increasing list of adverse effects, should not be used for routine therapy.

Allergic disorders in which H_1-receptor antaqonists may be useful

H_1-receptor antagonists provide relief of symptoms in patients with allergic rhinitis and/or allergic conjunctivitis, in allergic skin diseases, such as atopic dermatitis and urticaria, and in asthma and anaphylaxis. Their use in otitis media with effusion (OME), acute otitis media, or in upper respiratory tract infections (URI), although the use is widespread, is controversial. Formulations and recommended dosage of representative H_1-receptor antagonists are listed in Table 2.

Allergic rhinitis.

H_1-receptor antagonists are effective in the management of seaonal and perennial allergic rhinitis symptoms, such as rhinorrhea, nasal itching and sneezing.[48, 49] None of the H_1-receptor antagonists, including the new, relatively nonsedating medications, are highly effective in prevention of nasal blockage in antigen challenge tests,[50] and none relieve nasal blockage, as well as they prevent and relieve rhinorrhea, itching or sneezing. Addition of sympathomimetic, such as pseudoephidrine to an H_1-receptor antagonist significantly improves relief of congestion, compared to the relief of congestion achieved by the H_1-receptor antagonist alone.[51, 52]

Traditionally, all the first generation H_1 antihistamines are usually administered 3 or 4 times daily, but this type of dosage regimen is unnecessarily frequent of these medications, including chlorpheniramine and brompheniramine.[53, 54 55] The second generation H_1 antihistamine, terfenadine, is generally administered in a dose of 60 mg every 12 hours, but 120 mg every 24 hours is just as effective.[56]

There is renewed interest in topical application of H_1 antihistamine to the nasal mucosa. Topically applied azatadine inhibits the early release of histamine and concomitant symptom after antigen and histamine challenge intranasally.[57] Topically applied levocabastine, which has the highest potency of any H_1 antihistamine described so far, 15,000 times that of chlorpheniramine, provides signignicant protection against allergen-triggered allergic rhinitis symptoms.[58, 59]

H_1- and H_2 antihistamines administered simultaneously, topically or by mouth, are significantly more effective in blocking nasal congestion than either H_1 or H_2 antihistamine alone. The synergistic effects are not large, however, and have not been found in all studies: therefore, although these findings are of theoretical interest, they are probably not clinically important.[60, 61]

In prospective, controlled, double-blind studies, H_1 antihistamines are generally found to be less potent than topical corticosteroids in the treatment of allergic rhinitis symptoms.[62, 63] H_1 antihistamines are less potent than sympathomimetics, such as phenylpropanolamine or pseudoephedrine in the treatment of nasal congestion.[64, 65] No satisfactory comparison of H_1 antihistamine with

topical disodium cromoglycate in allergic rhinitis exists.

Allergic conjunctivitis.

In patients with allergic conjunctivitis, H_1 antihistamines, administered by mouth, are useful for the relief of ocular symptoms, such as itching, tearing, and erythema.[62, 63] Potent H_1 antihistamines, such as levocabastine, applied topically to the conjunctivae, also provide relief of allergic conjunctivitis symptoms.[66]

Allergic skin disorders (atopic dermatitis and urticaria)

H_1 antihistamine are commonly prescribed for symptomatic relief of itching in these disorders. Itching is difficult to quantify; nevertheless, it has been observed that H_1 antihistamines have a greater antipruritic effect in allergic skin disorders than in other types of pruritic skin disorders. The mechanism of the antipruritic effect is unknown, but it is not entirely peripheral.[67] In atopic dermatitis, hydroxyzine has a greater antipruritic effect than cyproheptadine.[25] Second-generation H_1 antihistamine, such as astemizole, are not as effective as hydroxyzine in relieving pruritus in atopic dermatitis, suggesting that the sedative effect provided by the first-generation H_1 antihistamine contributes to the relief of pruritus.

In suppression of histamine-induced wheals and flares and in suppression of dermatographism, hydroxyzine is more effective than other first-generation H_1 antihistamine, such as diphenhydramine, chlorpheniramine, promethazine, and cyproheptadine.[25] In patients with urticaria, it is genrally mentioned that hydroxyzine is superior to other first-generation H_1 antihistamines, in contrast to the author's own study which found that hydroxyzine was not better than chlorpheniramine in treatment of chronic urticaria.[45] In recent studies in adults with chronic idiopathic urticaria, the second genration H_1 antihistamines, such as terfenadine, astemizole, oxatomide and cetirizine have been well tolerated and have resulted in significant remission of symptoms, compared to the relief provided by placebo.[68, 76] A combination of H_1 and H_2 antihistamines may be beneficial in patients with chronic urticaria who do not respond to H_1 antihistamine alone.[45]

Bronchial asthma

In numerous well-designed, double-blind studies, H_1 antihistamines, such as chlorpheniramine, hydroxyzine, clemastine, terfenadine and cetirizine have been proved to have a modest, dose-related bronchodilator effect. In bronchial challenge studies, administered by mouth, intravenously, or by inhalation prevent histamine-, antigen-, hyperventilation-, and exercise-induced asthma[77-82] but not methacholine-induced asthma.[83] Azelastine which is promulgated chiefly for their antiallergic effect, also has strong H_1-reeptor antagonist action that may contribute to its bronchodilator action.[84]

H_1 antihistamines are not drugs of first choice for acute or chronic asthma, however, previous concerns about the potential adverse effects of H_1 antihistamine in asthma have been exaggerated. If H_1 antihistamines are required for chronic rhinitis treatment or for treatment of pruritus in patients with allergic skin disorders, they should not be withheld from patients with concurrent asthma.

Anaphylaxis

The initial treatment of choice for anaphylaxis consists of administration of epinephrine, a potent physiologic antagonist of the immediate hypersensitivity response, which prevents further mediator release and "turns off" the adverse reaction. H_1 antihistamines such as hydroxyzine or diphenhydramine, are useful adjuncts to epinephrine for control of pruritus, rhinorrhea, and other symptoms. However, an H_1 antagonist should never replace epinephrine, in the treatment of anaphylaxis. The hypothesis that an H_2 antihistamine, administered concurrently with an H_1 antihistamine to patients with anaphylactic shock might be more effective in treating

hypotension than an H_1 antihistamine alone requires further testing. An H_1 antihistamine can be used by hypodermic or intravenous injection in preparation in the patient who is allergic to Iodine contrast media who is going to have Iodine x-ray examination, in order to prevent anaphylactic shock from the procedure. However, intravenous administration of cemetidine and ranitidine is not without danger because these medications may cause asystolic if they are administered rapidly.

Otitis media

H_1 antihistamines, often in combination with sympathomimetics, are frequently prescribed for children with otitis media. Only a few well-designed, placebo-controlled, double blid studies in which there is repeated objective assessment of tympanic membrane compliance support the beneficial effects of these medications on eustachian tube function.[85]

OME has a high spontaneous remission rate. In one large study in children who had OME, a 2-week course of ampicillin was superior to a 4-weed course of a chlorpheniramine/pseudoephedrine preparation and to placebo.[86] Triprolidine, either alone or in combination with pseudo-ephedrine, did not shorten the course of chronic serous otitis media, although in patients treated with the combination of medications, the mean pressure gradient across the tympanic membrane was significantly improved.[87] compared to patients treated with triprolidine alone or with placebo.

In acute otitis media, H_1 antihistamines, such as chlorpheniramine and brompheniramine in combination with sympathomimetics, have generally not been demonstrated to provide statistically significant benefit in terms of resolution of symptoms or prevention of persistent middle ear effusion from developing,[88, 89] although in one double-blind study, chlorpheniramine, in combination with phenylpropanolamine and phenyltoloamine, was more effective than placebo.[90]

There is conflicting evidence as to whether H_1 antihistamines in combination with sympathomimetics prevent acute otitis media from developing in children with URI. In one-double blind study, the incidence of acute otitis media was almost identical in children who received placebo.[91]

Upper respiratory tract infections (URI)

Antihistamines used alone or in combination with other drugs have been promoted for treatment of viral URI since the late 1940s. Many of the studies suggesting their usefulness were conducted decades ago and were not randomized, double blind, placebo-controlled clinical trials. Although studies can be found in which H_1 antihistamines, such as chlorpheniramine or terfenadine, were apparently superior to placebo in ameliorating the symptoms of the common cold,[92, 93] other recent well-designed, placebo-controlled studies do not support the use of oral or topical H_1 antihistamines in prevention or relief of URI.[94]

Antihistamine selection

Antihistamines are frequently prescribed for symptoms of allergic rhinitis, allergic conjunctivitis, serous otitis media, pruritus in allergic skin disorders, and URI. Therapeutic program are often interrupted by complaints of drowsiness and other side effects caused by the antihistamines. Especially for patients with allergic diseases, who are likely to remain on antihistamines for a prolonged period of time, proper antihistamine selection is very important. The selection of an antihistamine that provides both adequate symptom relief and minimal side effects is made difficult by the marked degree of individual variation among patients to antihistamines.[95] Since it is a matter of individual variations, it is very difficult to indicate which antihistamine is the best, becuase one antihistamine can give the very good result in some patients but in the other patients who have the same disease may not get the benefit from this antihistamine at all.

The standard antihistamines with several different classes in order of increasing frequency of significant side effects are trimeprazine, chlorpheniramine, hydroxyzine, diphenhydramine, and tripelennamine.[96] Second-generation antihistamines produce less or no drowsiness in the patients, so they are preferrable to give to the patients who can not tolerate the side effects of standard antihisatmines, but the costs of the second-generation antihistamines are high, some poor patients are unable to buy them. In practice, the physician should start first with the cheap standard H_1 antihistamines, if there is no effect in relief the symptoms, then the antihistamines should be changed to the other standard antihistamine of the different class. If the patients are drowsy from the standard H_1 antihistamine, then the second-generation H_1 antihistamines should be considered. Remember that the physicain should prescribe the cheap, well-tolerated and effective antihistamine to the patients.

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