Anti-histamines: A classical treatment for Allergic conditions

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Abstract: *This article reviews information about H1 Antihistamines and the interaction of histamine with its H1-receptor and describes the concept that H1-antihistamines are inverse agonists it means that they produce the opposite effect to histamine on the receptor. The Advantages and disadvantages of antihistamines are discussed and also giving mechanism of action of antihistamines to show their therapeutic effect. It then shows the use of first-generation H1-antihistamines is not preferable in clinical practice today for two main reasons. First, they are having side effects and also less effective than second generation H1-antihistamines. There are many effective and safe second-generation H1-antihistamines in the market for the treatment of allergic conditions. Of the two drugs highlighted in this paper, levocetirizine and fexofenadine are the most efficacious in humans in vivo. However, levocetirizine may cause fatigue in susceptible patients while fexofenadine has a relatively short duration of action with twice daily administration of dose. While desloratadine is less effective, it has the advantages of rarely causing fatigue and having a long duration of action. All H1-antihistamines are showing anti- inflammatory properties but they requires regular dosing rather than dosing 'on-demand'.*

Key Words: *Anti histamines. H1 antihistamine, allergic treatment,*

1. 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.[1] Histamine exerts its effects in allergic diseases primarily by interacting with H1 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).[2] In chronic allergic inflammation, histamine has effects on inflammatory cells and causes cellular activation (mast cells, basophils and eosinophils) and the release of pro inflammatory mediators such as leukotrienes and cytokines Antihistamines are most often used to provide symptomatic relief of allergic symptoms caused by histamine release.[3] 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.[4]

2. HISTAMINES AND IT'S RECEPTORS[2]

Histamine is synthesized and released by different human cells, especially basophils, mast cells, platelets, histaminergic neurons, lymphocytes, andentero-chromaffin cells. It is stored in vesicles or granules released on stimulation. Histamine (2-[4-emidazolyl]ethylamine) was discovered in 1910 by Dale and Laidlaw and identified as a mediator of anaphylactic reactions in 1932. Histamine is a biogenic amines and it is synthesized from the pyridoxal phosphate and from the histidine amino acid it contains L-histidine decarboxylase enzyme. Histamine is a powerful intermediator of various physiologic reactions. The effect is exert by histidine on target cells in different tissues by binding to four receptors: histamine receptor HR1, HR2, HR3, and HR4. Table 1 summarizes the particularities of each one of these receptor types. These receptors belong to the G protein-coupled receptors family (GPCRs).[1] H1 receptor (HR1) is codified in the human chromosome and is responsible for many symptoms of allergic diseases, such as rhinorrhea, pruritus, contraction of the intestinal smooth muscle and bronchospasm. Activation of HR1stimulates the signaling

pathways of inositol phospholipid culminating in the formation of inositol 1,4,5-triphosphate (InsP3) and diacylglycerol (DAG), leading to an increase in intracellular calcium. Moreover, when HR1 is stimulated, it can activate other intracellular signaling pathways, such as phospholipase D and phospholipase A. Recently, from research it was shown that activation of the nuclear transcription factor by stimulation of H_1 receptor and both are involved in the development of allergic diseases.[6]

Histamine receptor	Cell and tissue expression	Activated intracellular signals	G Proteins
HR1	Nerve cells, airway and vascular smooth muscles, endothelial cells, hepatocytes, epithelial cells, neutrophils, eosinophils, monocytes, DC, T and B cells.	Main signaling: enhanced Ca2+ Others: PhLC, PhLD, cGMP, PhLA, NFκ B	$G_{q/11}$
HR2	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes DC, T and B cells.	Main signaling: enhanced AMPc Others: Adenylate cyclase, c-Fos, c-Jun, PKC, p70S6K	$G_{\pm S}$
HR3	Histaminergic neurons, eosinophils, DC, monocytes low expression in peripheral tissues. It inhibits histamine release and synthesis.	Main signaling: inhibition of cAMP Others: enhanced Ca2+, MAP kinase.	$G_{i/o}$
HR4	high expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DC, T cells, basophils, mast cells, low expression in nerve cells, hepatocytes peripheral tissues, spleen, thymus, lung, small intestine, colon and heart. It stimulates chemotaxis of eosinophils and mast cells.	Enhanced Ca2+, inhibition of cAMP	$G_{i/o}$

Eos, eosinophils; B cells, B lymphocytes; T cells, T lymphocytes; PKC, protein kinase C; cAMP, cyclic adenosine monophosphate; PhLC, phospholipase C; PhLD, phospholipase D; PhLA, phospholipase A; NF_B, nuclear transcription factor Kappa
Adapted source: Jutel M, et al. [1]

Table 1: Different Histamine Receptors

Histamine H1-receptors

The histamine receptor (H_1) is a member of the family of G-protein coupled receptors. This superfamily having common structure of 7 transmembrane helical segments (Fig. 1) and represents at least 500 individual membrane proteins. The histamine H1-receptor gene encodes a 487 amino acid protein which having molecular mass of 55.8 kDa. The histamine H1-receptor, may be viewed as "cellular switches like other G-protein coupled receptors," which exist as an equilibrium between the inactive or active state i.e. off or "on" state. In the case of the Histaminergic H1-receptor, stabilize the receptor in its active conformation in histamine cross-links sites on transmembrane domains III and V, thus causing the equilibrium to swing to the on position.[8] H1-antihistamines, do not antagonize the binding of histamine but bind to different sites on the receptor to give the opposite effect which are not structurally similar to histamine,. Thus, H1-antihistamines are not antagonists of receptors but they are inverse agonists in that they produce the inverse effect on the receptor to histamine. Consequently, the proper term to define these drugs is "H1 antihistamines" rather than "histamine antagonists."[7]

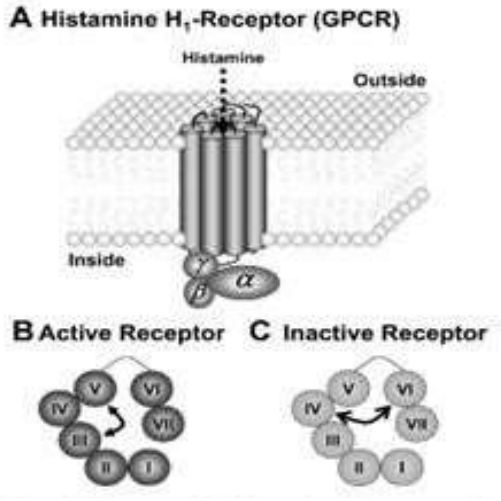
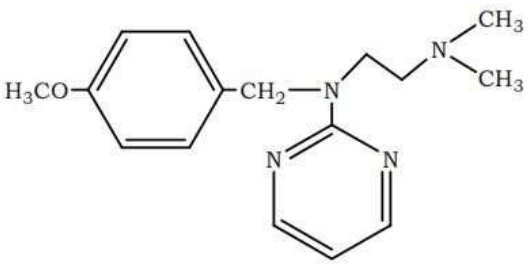


Figure 1: Histamine H1- receptor in a membrane showing 7 transmembrane domains

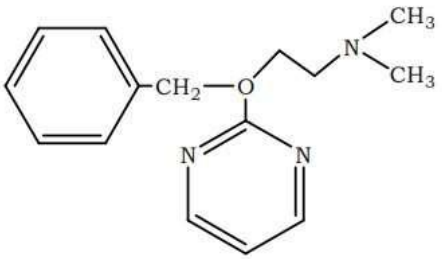
3. FIRST-GENERATION H1-ANTIHISTAMINES:

The Source of First-generation H1-antihistamines are from identical chemical stem from that cholinergic muscarinic antagonists, antihypertensive, tranquilizers, and antipsychotics drug agents were simultaneously developed, they have poor receptor specificity and sometimes interact with receptors of different biologically active amines producing antimuscarinic, anti–adrenergic, and antiserotonin effects.[9] But maybe their greatest disadvantage is their ability to cross the BBB and interfere with histaminergic transmission. Histamine is a very important neuromediator within the human brain that contains just about 64,000 histamine-producing neurons, situated within the tuberomamillary nucleus. When activated, these neurons stimulate H1-receptors in all of the major parts of the cerebrum, cerebellum, posterior pituitary, and spinal cord where they increase arousal in the circadian sleep/wake cycle, reinforce learning and memory, and have roles in fluid balance, suppression of feeding, control of temperature of body, and also control on cardiovascular system, and conciliation of stress trigger release of adrenocorticotrophic hormone and endorphin from the pituitary gland. It is not shocking then that antihistamines crossing the BB Barrier interfere with all of those processes.[1]

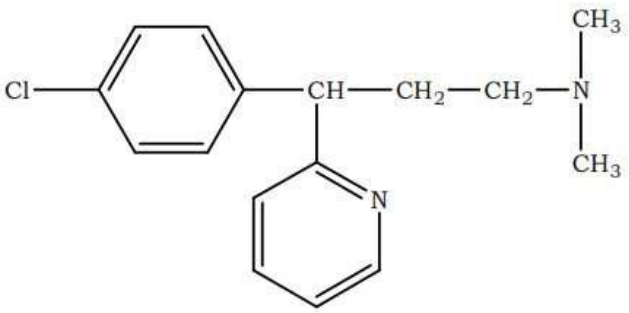
Thonzylamine



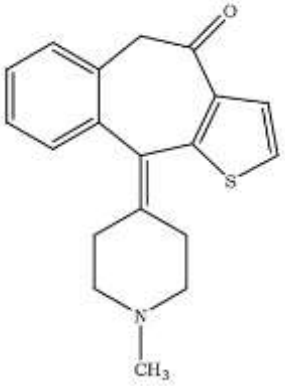
Diphenhydramine



Chlorpheniramine



Ketotifene

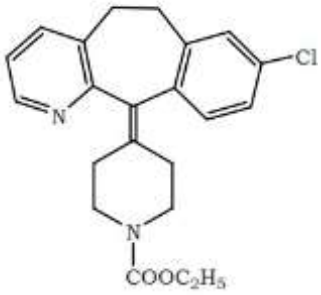


Physiologically, the arousal is caused because of the discharge of amine throughout the day whereas its production attenuated at night-time ends up in a passive reduction of the arousal response. once first-generation H1- antihistamines are taken throughout the day even within the manufacturers' suggested doses, often times cause day time temporary state, drowsiness, fatigue, sedation, and impaired concentration and memory.[3] once first-generation H1- antihistamines are taken in night then it'll will increase the latency to the onset of speedy eye movement sleep and cut back the period of fast eye movement sleep. The residual effects together with impairment of attention, poor sleep, vigilance, remembering, and sensory-motor performance, also are their subsequent morning. Impairment of the power of adults to do work, drive, and fly craft are effects of first-generation H1-antihistamines on learning and examination performance the in kids and are reviewed well in a very recent review. In young children's the employment of first- generation H1-antihistamines has recently been brought into question. within the U.S., reports of significant and sometimes dangerous adverse events of promethazine in kids lead to a "boxed warning" being included in 2004 to the labelling of promethazine. The warning included a reason to be used in kids younger than two years and a strong warning with relevancy use in kids two years aged or older. In Feb 2009, the Medicines and health care products Regulatory Agency (MHRA) within the U.K. suggested that cough and cold remedies containing sure ingredients, including first- generation H1-antihistamines, should not be utilized in children younger than half dozen years as a result of the balance of benefit and risks has not been shown to be favorable. Reports submitted to regulators expressed that over 300 individuals have reported adverse reactions to those medicine which diphenhydramine and chlorpheniramine were mentioned in reports of 27 and 11 deaths, respectively.[10]

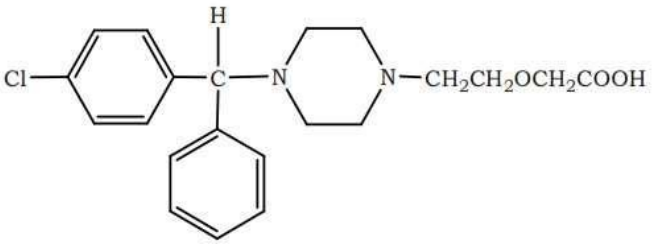
4. SECOND-GENERATION H1-ANTIHISTAMINES:

In 1980s Antihistamines are becomes very advance with the introduction of second-generation H1-antihistamines, which are very less sedating or on-sedating because of their penetration of the blood brain barrier is limited.[11] In addition, these drugs are highly specific for the histamine H1-receptor and also not shows anticholinergic effects. When selecting an H1-antihistamine as a medicament patients view attributes that include good efficacy, a rapid onset of action, a long duration of action, and freedom from unwanted effects. Although this is predicted from preclinical and pharmacokinetic studies, it is only in the clinical environment that they may be definitively established.[12]

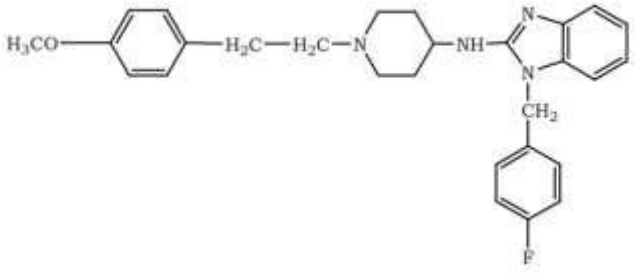
Loratadine



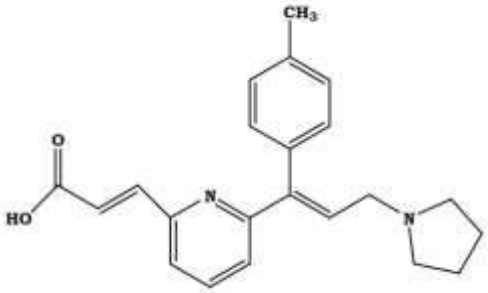
Cetirizine



Astemizole



Acrivastine



H2- ANTIHISTAMINES

H2-antihistamines occur as inverse agonists and neutral antagonists like H1 antihistamines. They act on H2 histaminergic receptors which are mainly in the parietal cells in the gastric mucosa, and it is an important part of the endogenous signalling pathway for gastric acid secretion. Normally, Acid secretion stimulate by the acting histamine on H2 receptor; drugs reduces acid secretion by inhibiting H2 signalling. for gastrointestinal conditions H2-antihistamines are among first-line therapy including peptic ulcers and gastroesophageal reflux disease. Some over the counter formulations are also available. Cross-reactivity with unintended receptors may causes most of side effects. For example, Cimetidine is notorious for antagonizing androgenic testosterone and DHT receptors at high doses.[11]

MECHANISM OF ACTION

Mast cells secretes the histamine and it binds with histaminergic receptors (H1, H2, H3 or H4) to elicit a series of events mediates the characteristic response through second messenger systems. The type of all histaminergic receptors are G-protein coupled receptor. The formation of IP3 and DAG is by the activation of H1 receptors coupled with Phospholipase-C, respectively from phospholipids in cell membrane. Formation of IP3 leads to rapid release of Ca2+ from endoplasmic reticulum. DAG activates the protein kinase C, altogether turnover of Ca2+ and protein Kinase-C activates Ca2+/calmodulin dependent protein kinase and phospholipase A2. H1 antagonist binds with H1 receptors, it decreases the production of Phospholipase-C and activates the IP3 and DAG there by blocks the characteristic response of histamine. H2 receptor produces cAMP-dependent protein kinase to elicit the response in Gastro intestinal tract. The H2 receptor bind reversibly by H2 antagonist and reduces the cAMP formation. Further, it is responsible for the activation of proton pump and afterwards reduces the stomachic acid secretion in GIT. H3 receptors also are G-protein coupled receptors, unlike H1 and H2. The receptors produce a decreased Ca2+ influx. H3 receptors function as feedback inhibitors for histamine and other neurotransmitter by decreasing the Ca2+ influx into the cells in CNS and GIT. [7]

PHARMACODYANAMIC

The pharmacokinetics and pharmacodynamics of the second-generation antihistamines when compared with the information available on the first-generation agents for the approval of a new medication have led to the availability of much

more information for This consideration alone would advise the more widespread use of the second-generation antihistamines.[14] All H1 antihistamines are reversible, competitive inhibitors of First-generation H1receptors. First-generation H1 antihistamines act both on peripheral and central H1 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 H1 antihistamines (e.g. promethazine) has an adrenergic blocking activity, which may cause hypotension. 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 H1-receptor site avoids the potential for adverse effects on the CNS.[3] There are six structural classes of antihistamines (Table 2). 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. [4]

Alkylamines	Ethanolamines	Ethylenedia	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	Cetirizine Levocetirizine

Table 2: Structural classes of H_1 Antihistamines

PHARMACOKINETICS

When selecting an antihistamine for a particular patient, the pharmacokinetics of the various antihistamines needs to be considered (Table 3). The good absorption show most of antihistamines when administered orally, as is demonstrated by the fact that effective plasma concentrations are usually reached within 3 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 and fexofenadine avoid this metabolic passage through the liver to a vital degree. fexofenadine is eliminated in stools following excretion by the biliary tract while cetirizine and levocetirizine are eliminated in urine, mainly in unaltered form.[3] The conventional H1 antihistaminic are well absorbed from oral and parenteral routes, metabolized in the liver and excreted in urine. They are widely distributed in the body and enter brain. The newer compounds penetrate brain poorly accounting for their low/absent sedating action. Duration of action of most agents is 4–6 hours, except meclozine, chlorpheniramine, mesolastine, loratadine, cetirizine and fexofenadine which act for 12–24 hours or more.[4]

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,	20 hours	SR: 8 mg every 12 hours or 4 mg every 6 to 8 hours
Clemastine	2 hours	No (conjugation)	anticholinergics,	10-12 hours	1 mg twice daily

Diphenhydramine	2 hours	Yes (CYP2D6)	CYP2D6 enzymes	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					
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	Ye	Possible	12.9 hours	10 mg once daily

Table 3: Pharmacology of the currently available H1 antihistamine used in allergic

PHARMACOTHERAPY

Allergic rhinitis

Antihistamines are most beneficial in the management of nasal allergies. In patients with allergic rhinitis, H1 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. [15]

Vertigo

Cinnarizine is the H1 Antihistamine having additional properties like anticholinergic, anti-5-HT, and vasodilator which has been widely used in vertigo. It modulates Ca^{2+} fluxes and attenuates vasoconstrictor action of many endogenous mediators. Cinnarizine inhibits vestibular sensory nuclei in the inner ear, suppresses postrotatory labyrinthine reflexes, possibly by reducing stimulated influx of Ca^{2+} from, endolymph into the vestibular sensory cells. Beneficial effects have been reported in Méniére's disease and other types of vertigo. Side effects are sedation and mild g.i. upset. Dimenhydrinate is another effective antivertigo antihistaminic.[4]

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. [4] Although oral antihistamines may be effective, symptoms of allergic conjunctivitis are often best managed with an ophthalmic preparation. [3]

Urticaria

Irrespective of the cause of the urticaria, the less sedating antihistamines are the mainstay of the treatment.[5] Chronic urtication may be a long condition within which spontaneous mastocyte degranulation and will occur in conjunction with numerous sorts of physical urticaria caused by exposure to: water (aquagenic), sun (solar), cold, prolonged pressure (delayed pressure urticaria). These patients may display dermatographism., The newer antihistamines can be used for treatment or prophylaxis for patients with physical urticaria. They sometimes need up to fourfold the suggested dose for

this treatment. The less sedating H1 antihistamines also are the mainstay of treatment for chronic spontaneous urtication. This is outlined by the looks of hives a minimum of a couple of times every week for over six weeks. Antihistamines are most effective when dosed regularly (twice a day) to prevent the onset of hives, rather than waiting for their appearance. In some cases, antihistamines can be used at up to four times the recommended dose. If H1 Antihistamines are not effective then H1 antihistamines such as famotidine and ranitidine (which block the Histamine receptors found in the stomach, vascular smooth muscle and elsewhere) can be used.[12]

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.[3] 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 sub-therapeutic 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.[3]

Tachyphylaxis

There is a widespread belief in the community that taking long-term antihistamines makes them less effective and that it is better to swap between different types of antihistamines for the best effect. There is no compelling proof that tachyphylaxis happens with the newer H1 antihistamines. A recommendation to swap treatment isn't contained in any of the position statements of the key societies which give recommendation regarding medicine use. Multiple studies have shown that the effectiveness of the newer medicine in ameliorating the effect of amine release within the skin continues unchanged for up to 30 to 180 days. Patients may mistake an intensification of the underlying symptoms for a waning in effectiveness of the antihistamine. There are situations in which a pre-emptive intensification of treatment may be required such as before contact with a known trigger or in the weeks before the onset of the spring pollen season. However, this intensification of treatment is often achieved by magnified doses of the patient's usual medicine and doesn't ought to involve a modification to a brand new medicine that may cause idiosyncratic reactions.

SIDE-EFFECTS

Central nervous system

H1receptors are widely distributed throughout the CNS and the first-generation H1antagonists 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. [3]

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 metabolized 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 H1receptor and appear to be limited to terfenadine and astemizole. Other second-generation antihistamines, such as cetirizine, fexofenadine and levocetirizine, which are minimally metabolized, are safer alternatives.[3]

6. CONCLUSION:

From the study it is concluded that first generation anti histamines are less effective than second generation anti histamines and they also cause some severe side effect on patient's body which are not gives by second generation antihistamines. There are so many second generation antihistamine with effective and safe treatment for allergic diseases. All anti histamines possess anti-inflammatory property and it require regular doses rather than at a time of demand.

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