American Journal of Medicine and Medical Sciences 2014, 4(6): 236-240
DOI: 10.5923/j.ajmms.20140406.07

H1 Antihistamines as Antiallergy Drugs

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Abstract This paper basically reviews the definition of histamine and how it is released that it targets four different types of receptors coming from the G-protein receptor family. Each receptors has its own distribution of cells causing symptoms of allergic reactions such as asthma, headaches, flushing, erythema and others as well. This review addresses the therapeutic benefits of H1 antihistamines in general to relieve allergic reactions symptoms as we know that allergic reactions cannot be cured. Generally, the aim of this paper is to acknowledge the pharmacology of antihistamines including pharmacokinetic and pharmacodynamic. Infact, there are two classes of H1 antihistamine, including first and second generation and how it can be differentiated based on their action of drug in the body. Liposolubility is the main factor that plays an important role in access to permeability across the cell membrane. Pharmacokinetics of antihistamines includes the ways of H1 antagonist absorb depending on its duration and type of drug, where is it metabolized and how it is eliminated from the body in order not to accumulate the drug in the tissues. Pharmacodynamic of antihistamines simply means the effect of H1 antagonist, for instance antinausea or sedating effect. This paper also describes the adverse effects of HI antihistamines if it is not properly used especially those obtaining from the OTC whom fail to read the warning label which has resulted in many unfortunate events as for such traffic accidents and injuries. At the current situation studies have shown that doctors nowdays often prescribed loratadine and cetrizine, both of which are of a newer generation of antihistamine as a the most safest and preferable choice in treating allergic reactions in both children and adults.

Keywords Antihistamine, Allergy, Sedative

1. Introduction

H1 antihistamines including the first and second generation can be differentiated by their chemical structure and potential toxicity [1, 2]. Generally, the older generation has more adverse effects compared to the new generation of antihistamines [1, 2]. The allergen binds to IgE surfaces where the release of most histamine binds to H1 receptor to induce erythema and itching causing allergic reactions to occur [3, 4]. Histamine released has a set of different effects on different target organs for example in the nervous system, cardiovascular system, bronchiolar smooth muscle and etc [5]. They have been used to treat and relieve symptoms of various types of allergies including airway disorders such as asthma or upper respiratory tract infection, allergic rhinoconjunctivitis, urticaria and also the most severe systemic allergic reaction known to be anaphylaxis [6].

Antihistamines play a major role in allergic inflammation by inhibiting abundant mediators such as mast cells and basophils in response to the immune system [6]. There are more than 40 H1 antihistamines which are assumed to be efficient and safe by health professionals but however, they do have adverse side affect or potential toxicology if taken excessively hence needing proper use as much as selection dosage of antihistamine also matters [1, 6]. Generally, second generation is the most preferable choice particularly loratadine and cetrizine which are available at 10mg tablet or 10ml liquid form respectively that can be given to both children and adults as it has a less sedating effect and drowsiness compared to the first generation antihistamines [7].

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Published online at http://journal.sapub.org/ajmms

2. Literature View

2.1. Biochemical Background of Histamine

Histamine is synthesized from L-histidine by the enzyme, histidine decarboxylase which consists of 4 types of receptors mainly H1, H2, H3 and H4 that can be differentiated based on their distribution affecting on different target organs [4, 6]. Most H1 receptors are distributed at the smooth muscles, endothelium and brain [4]. For example, if histamine binds to H1 receptor at the bronchiolar smooth muscle it causes bronchoconstriction inducing spasm at the lung airway causing difficulties in breathing when an individual has allergic reactions [4]. H1 receptor is specific for H1 antihistamine localized on the chromosome 3 in humans [5, 6].

Most bound histamine is in the inactive form therefore

they transduce signals through G- proteins and secondary messengers such as calcium channels, diacyglycerol, phosphoinositol triphosphate and etc [4-6]. The figure below shows the effect of agonist and antagonist of histamine where there is a shift from either towards the active or inactive state respectively [6]. Antihistamine is most known to be an inverse agonist where there will be a shift of equilibrium from the active to the inactive state due to its inactivation of intracellular messengers that contributes to predominance of stabilized inactivated conformation of the active receptor [3, 6].

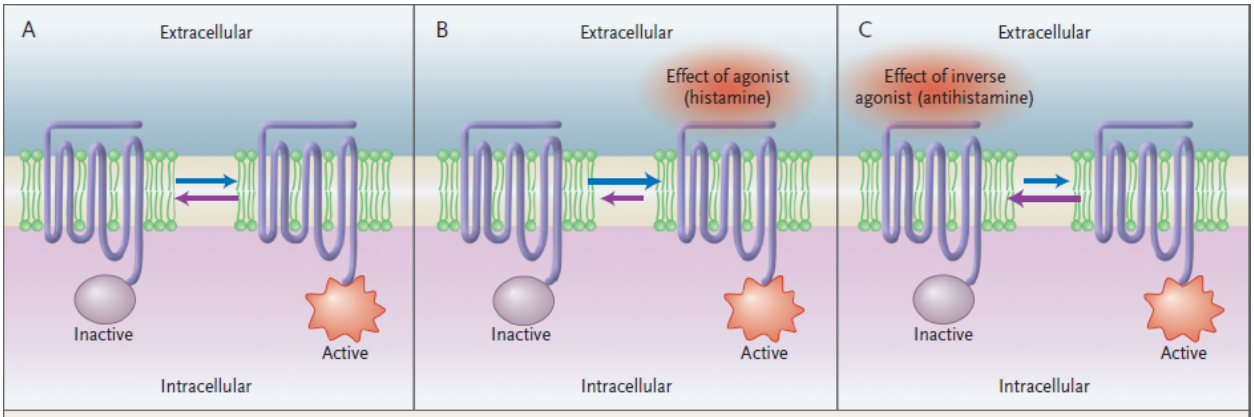

Figure 2. Simplified Two-State Model of the Histamine H_1-Receptor.

In Panel A, the inactive state of the histamine H_1-receptor is in equilibrium with the active state. In Panel B, an agonist, which has a preferential affinity for the active state, stabilizes the receptor in this conformation and consequently causes a shift in the equilibrium toward the active state. In Panel C, an inverse agonist, which has a preferential affinity for the inactive state, stabilizes the receptor in this conformation and consequently causes a shift in the equilibrium toward the inactive state. All known H_1-antihistamines function as inverse agonists. Intracellular and extracellular are defined in relation to the cell membrane. The purple serpentine line denotes the G-protein–coupled receptor, and green the cell membrane. Adapted from Leurs et al.[25]

Figure 2. Simplified Two-State Model of the Histamine H_1-Receptor

Table 2. Chemical and Functional Classification of H_1-Antihistamines

Chemical Class	Functional Class	
	First-Generation Drugs	Second-Generation Drugs
Alkylamines	Brompheniramine, chlorpheniramine, dimethindene,*† pheniramine,† triprolidine	Acrivastine
Piperazines	Buclizine, cyclizine, hydroxyzine, meclizine, oxatomide*	Cetirizine, levocetirizine*
Piperidines	Azatadine, cyproheptadine, diphenylpyraline, ketotifen†	Astemizole,* desloratadine, ebastine,* fexofenadine, levocabastine,† loratadine,‡ mizolastine,* olopatadine,† terfenadine*
Ethanolamines	Carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, phenyltoloxamine*	—
Ethylenediamines	Antazoline, pyrilamine, tripelennamine	—
Phenothiazines	Methdilazine, promethazine	—
Others	Doxepin§	Azelastine,† emedastine,† epinastine†

* In the United States, this H_1-antihistamine is either not yet approved, has never been approved, or has had approval withdrawn.
† Topical H_1-antihistamines are applied to the conjunctivae, the nasal mucosa, or both. Some of them are available in oral formulations in some countries.
‡ In the United States, loratadine became available over the counter in 2003, and the change in status had a major effect on physicians' prescribing patterns and on the costs of the medication to patients. Other second-generation H_1-antihistamines are available only by prescription.
§ This medication has H_1- and H_2-antihistamine activities and is also classified as a tricyclic antidepressant.

The table below shows that H1 antihistamine can be classified into first generation which is more sedating compared to second generation due to its more permeable access into the central nervous system [2, 4, 6]. However, the first generation maybe a preferable choice for some people especially if their occupation needs constant alertness [2, 4, 6]. Example of the first generation includes diphenydramine, chlorpheniramine and doxylamine and second generation includes cetrizine, loratadine and fexofenadine [3, 6]. The different forms of antihistamine could appear in the form of tablets, capsules, liquids, nasal sprays or eye drops [2]. Certain antihistamines can be obtained from OTC (over the counter) but some are only available by prescription for example antihistamines such as desloratadine, azelastine, levocetrizine and etc [2].

2.2. Role of Histamine

When allergic inflammation occurs where the allergen binds to the IgE surface, main mediators such as basophils and mast cells as well as other mediators such as prostatglandins and leukotrienes will release histamine to bind with H1 receptors in the skin causing edema formation and erythema leading to an increase of the heart beat and vasodilation prior to the effect of histamine in the cardiovascular system [4-6].

Histamine also exerts proliferation of Th1 cells hence functioning as a proinflammatory activity by releasing cytokines and lysosomal enzymes blocking the humoral immunity and may cause autoimmune or malignant disease through the H1 receptor [6]. Hence, antihistamine functions mainly to inhibit mediator release that is involve in the reduction of calcium intracellular activity that serves as an antiallergic effect purpose [6]. On the other hand, it also has an antiinflammatory effect that inhibits the cytokines and adhesion molecules [6].

2.3. Pharmacokinetic & Pharmacodynamic of Antihistamine

As for the pharmacokinetic of antihistamine, it has a good absorption where the peak concentration occurs within 1 to 2 hours when given orally [3]. They can be categorized into short acting and long acting antihistamines given the duration of action is about 4 to 6 hours and 12 to 24 hours respectively [4]. Generally, the long acting antihistamines are mainly in use for the chronic long term allergic reactions [1]. The absorption of antihistamines are determine by two factors which liposolubility is the main factor [3].

Most H1 antihistamines are able to dissolve the positive charge at the end of the liposoluble molecule that makes it easier to penetrate across the cell membrane and to the central nervous system [3]. Therefore, it causes drowsiness and this contributes the effect of a first generation antihistamine [3]. Secondly, P glycoprotein are active transporters that can be found on cell membranes which they can behave in two ways [3]. In a good way, it could function as drug clearance for example the drug cetrizine is not easily permeable across the cell membrane thus, lesser sedating effect but it also could have possible drug interactions [3, 6]. For example, if antihistamine is given with a cytochrome inducer such as benzodiazepine, it will counter effect antihistamine which reduces the clinical efficacy of antihistamine but increasing the benzodiazepine effect even more which could lead to the state of coma [3, 6].

Most metabolization of antihistamines occur in the liver by a group of enzymes belonging to the P450 cytochrome family but there are several that bypasses the liver metabolization [3]. For example, cetrizine and levocetrizine is eliminated through the urine and fexofenadine is eliminated through the stools by the billiary tract [3]. Inducers of cytochrome P450 such as benzodiazepine could also reduce plasma concentrations of H1 antihistamines but at the same time if there are cytochrome P450 competititors such as macrolides or antifungals, it could function vice versa by increasing its plasma concentration and causing adverse effects to occur at the central nervous system as well [3, 4].

Majority of the antihistamines binds to 95% of plasma proteins [3]. Therefore, they are easily accessible through the blood stream [3]. Hence, they are needed in smaller dose amounts to avoid drug accumulation in the liver or heart or toxicity in the cells [3]. HI antihistamines predominantly are expressed in many cells in the body such as smooth muscles, endothelial and epithelial cells and etc depending on the various type of receptors that releases these mediators on the cell membrane [3, 4]. These mediators acts on the targeted organs which are mediated by G protein and second messengers for example inositol triphosphate, DAG and etc [3, 4]. In addition, NF-KB transcription factors will be activated through the regulation of adhesion molecules and cytokine production [3].

Antihistamine is eliminated through the kidneys after metabolization in the liver [3]. Therefore, a careful dose adjustment is needed especially in patients whom are having kidney or liver disease since they are unable to metabolize or eliminate the drug and this could cause accumulation of antihistamine in the blood stream causing adverse effects as well [3]. As for the pharmacodynamics of H1 antihistamine, the first common effect is sedation especially applies with the first generation like diphenydramine [4]. Antihistamine such as doxylamine can be used to treat nausea and vomiting as it has an antiemetic function especially during pregnancy and motion sickness [4].

Many H1 antagonists demonstrate the adrenoreceptor-blocking actions where for example, promethazine from the phenothiazine class could cause orthostatic hypotension in some individuals if taken at large dosage [4]. H1 antagonist not only blocks histamine receptors but also blocks serotonin for example cyproheptadine where it could produce an adverse effect in which by increasing the appetite of that individual and there will be a decrease in the energy expenditure hence leading towards obesity [4, 6]. Other than that, it also has an antiparkinsonism effect where antihistamine such as diphenydramine can be used for the suppression of extrapyramidal effects such as dystonia

reactions in psychotropic [6].

2.4. Adverse Effects of Antihistamine

Most people fail to read the warning signs of most antihistamines especially the first generation such as diphenydramine and chlorpheniramine that could be easily obtained from OTC that causes central nervous toxicity such as drowsiness, agitation, headaches and for mothers who consume it before parturition, it may cause the exact same symptoms in nursing infants [6]. If it is taken multiple and not treated in time, death may occur within hours [6].

As a result, it is prohibited among pilots and military before or during flights where traffic accidents, deaths in aviation or injuries are prone to happen [6]. In addition, it should not be taken with alcohol or tranquilizers as it can alleviate the sedative effects even more [1]. Hence, antihistamine is best to be taken before bedtime and not during the day especially those whom are having jobs that require constant alertness for example driving or while operating dangerous machinery [1, 2]. The abuse of antihistamine such as diphenydramine can result in euphoria or even hallucinations [6].

There are certain antihistamine that could cause teratogenicity in pregnancy especially those categorized in FDA category B and C for example diphenydramine and cetrizine belonging from the first generation and second generation respectively [6]. Hence, it is always best to consult the doctor before consuming antihistamine especially when you are having any medical illness or even breastfeeding [1]. Antihistamines should not be given to patients with organic heart disease such as ischemia, cardiac arrhythmias or electrolyte imbalance as it causes blockade of the cardiac ion channel known as delayed rectifier potassium channel which prolongs QT interval hence leading towards ventricular arrhythmia [6].

2.5. Comparing Effectiveness and Safety

There is a long debate on which to use or which is a better antihistamine [7]. Some older people prefer the first generation antihistamines as it works better for them and some prefer the newer antihistamines also known as the second generation due to its lesser sedative effect [7]. The second generation is said to be a better choice which consists of loratadine and cetrizine in treating allergic reactions not only because most doctors prescribed it but also due to its less sedating effect and it is said to be safer as it causes less drowsiness compared to the older generation of antihistamines [7].

Both loratadine and cetrizine can be obtained easily over the counter but in comparison, loratadine will be the best choice of antihistamine in both children and adults as some studies have analyzed that cetrizine also has a sedating effect and an increased risk in abnormal heart rhythm [7]. Both, loratadine and cetrizine can be obtained in a dosage of about 10mg in tablet and also 10ml liquid form at the market [7]. Loratadine can only be given to children aged 2 years and above but cetrizine can be given to children as young as 6 months and older [7]. The dosage for children will be the same as the adult dosage which is 10mg daily or one tablet a day but depending on the doctor's prescription it can also be reduced to a dosage of 5mg daily or half a tablet a day depending on the severity of the allergic reactions whether is it mild, moderate or severe but adults should keep an eye on their children for drowsiness [7]. For adults above 60 years old, they are much more susceptible to the side effects of antihistamine such as drowsiness, hence they should be careful as they have a greater risk in falling so the dosage has to be reduced for them especially if they are having any kidney or liver disease [7]. Sometimes, loratadine and cetrizine comes in dissolvable tablets specifically for young children or even for older adults that might have a problem in swallowing [7].

3. Conclusions

After discussing the points of view, it has been concluded that antihistamine does play a big role in inflammation and immunomodulation especially in allergic reactions by reducing mediator release and cytokine expression by blocking the predominant receptors on the cell surface membrane. However, it has to be used wisely and properly as it causes adverse effects mainly drowsiness as it could interfere with one's daily life activities. Therefore, it is important to always consult the doctor or read the warning label at the back of the bottle in order to know the effect of the medication to avoid any accidents such as injuries, traffic accidents and whether there is a possible drug interaction mainly in pregnancy or nursing infant especially when it is prescribed over the counter. Last but not least, loratadine is to be the best and safest drug treating allergic reactions both in children and adults and is commonly the most preferable choice of prescription among the doctors.

ACKNOWLEDGEMENTS

First of all, I would like to show my gratitude to the Lord because with his blessings I have managed to complete my paper entitled "H1 Antihistamine as Antiallergy Drugs".

With pleasure, I, **Rukshana Balakrishnan**, would like to convey my heartiest thank you to **dr. Ida Ayu Ika Wahyuniari, M. Kes,** the supervisor for my paper work whose encouragement, guidance, and support from the initial to the final level enabled me to develop an understanding of the topic and successfully complete my paper work.

I would like to apologize if there are any weaknesses that could be found in my report and I would be glad to get feedbacks from the readers as it would help me in improvising myself in time to come. Last but not least I hope that my writing would be beneficial to the readers as how it was for me.

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