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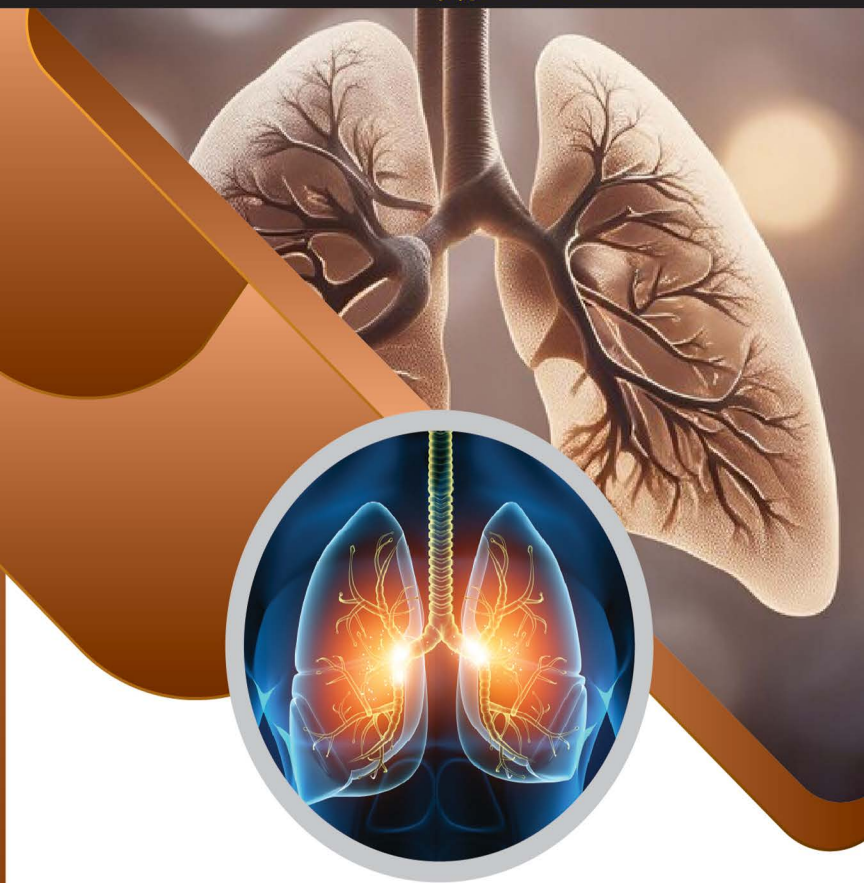

Drugs in RESPIRATORY MEDICINE

Jyotirmoy Pal
Nandini Chatterjee

JAYPEE

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3

CHAPTER

Prescribing Antihistamines in Allergic Disorders: Clinical Pharmacology Review

Shambo Samrat Samajdar, Debajyoti Saha, Sougata Sarkar

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INTRODUCTION

Endogenous histamine, an autacoid, plays an important role in immediate allergic response. Recent studies say histamine is a modulator of neurotransmitter release both in central and peripheral nervous systems. There are four types of histamine receptors, namely H1, H2, H3 and H4, which are responsible for different actions of histamine. All the four receptors are G protein-coupled receptors and none share any structural resemblance with each other. H1 and H2 receptors are postsynaptic and are located on cell membrane of Neuro Effector Junction. H3 behaves as an autoreceptor, is located presynaptically, and decreases histamine release from histaminergic neurons. H4 receptors are present on eosinophils, neutrophils, and CD4+ cells; and play a role in chemotaxis of white blood cells. H1 receptor-mediated action includes bronchoconstriction, spasmodic contractions of ileum and uterus, increased secretions from exocrine glands, mediating pain and itching, and mediate the maintenance of wakefulness. Stimulation of both H1 and H2 receptors causes vasodilatation mediated by the release of NO positive chronotropic effect on heart, and "triple response" characterized by flush, wheal, and flare. H2-mediated action causes release of gastric acid from gastric parietal cells.

The H1-antihistamines (AHs) are agents being widely accepted for treating different allergic conditions such as allergic rhinoconjunctivitis, asthma, and urticaria.[1] First-generation AHs (namely brompheniramine, chlorpheniramine, diphenhydramine, hydroxyzine, ketotifen, oxatomide, pheniramine, and pyrilamine) are

nonselective in their action because they bind to all H1 receptors, especially to those of Central Nervous System (CNS) causing sedation. Thus, nonselective AHs have been associated with impaired sleep, learning, and work performance and with motor vehicle, boating, and aviation accidents.[2]

To overcome the unfavorable risk-benefit profile of first-generation AHs, second- and third-generation AHs were introduced, which have better tolerability and lesser sedative property. According to several clinical trials, newer-generation AHs are considered to be safe, with prolonged duration of action, faster in onset, and potent in comparison to first-generation AHs. However, the cost of second-generation AHs remains as a barrier despite of its efficacy, potency, and safer side effect profile. Newer-generation H1AHs and second- and third-generation nonsedating AHs were developed with reduced blood–brain barrier penetrability and without anticholinergic effects. The second- and third-generation AHs (bilastine, cetirizine, desloratadine, ebastine, epinastine, fexofenadine, loratadine, levocetrizine, mizolastine, olopatadine, and rupatadine) are more selective in their action and lesser CNS penetrability than their first-generation AHs; thus, sedation is less. Second- and third-generation AHs have long half-life and are prescribed once daily dosing, improving patients' compliance.[3-5]

MECHANISM OF ACTION OF ANTIHISTAMINES

All current "antagonists" for the H1 receptor are indeed inverse agonists that diminish the receptor's constitutive activity and competing with histamine. While histamine attachment to the receptor causes a completely active state, AH binding gives an inert conformation. At the tissue level, the action noticed is proportionate to receptor occupancy by the AH. Most H1 antagonists have comparable pharmacological activities and therapeutic uses. Their effects are essentially predicted based on understanding of the effects of histamine's activation of H1 receptors. **Table 1** suggests actions of AHs in different targets. **Figure 1** has described affinity of different AHs with H1, H2, serotonin, alpha-adrenergic and cholinergic receptors. Second-generation AHs could not cross blood-brain barrier and do not exhibit extra-H1 actions.

Common side effects of first-generation AH are:

- *CNS suppression*: Sedation, poor sleep quality, and decreased cognitive performance. First-generation AHs are commonly used as sedatives because of their strong sedative qualities. However, these agents do

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TABLE 1: Action of antihistamines (AHs) on different targets.

Smooth muscles	H1 antagonists block histamine's effects on smooth muscles, specifically respiratory constriction. AHs block both the vasoconstrictor and vasodilator actions of histamine due to nitric acid (NO) synthesis or release. An H2 antagonist reduces residual vasodilation caused by H2 receptors on smooth muscle. AHs reverse histamine-induced increases in systemic blood pressure
Capillary permeability	AHs prevent histamine-induced enhanced capillary permeability, edema, and wheal
Flare and itch	AHs inhibit the effect of histamine on nerve terminals, including the flare component of the triple response and itching generated by intradermal injection
Exocrine glands	AHs do not inhibit gastric secretion; nevertheless, they inhibit histamine-induced salivary, lacrimal, and other exocrine secretions with varying efficacies. Furthermore, the antimuscarinic effects of several AHs may lead to decreased secretion in cholinergically innervated glands and reduced continuing production in, for instance, the respiratory tree. Nasal sprays of several AHs can be used to treat allergic rhinitis
Immediate hypersensitivity reactions: Anaphylaxis	Histamine is one of the numerous potent autacoids produced during hypersensitivity responses, and its proportional contribution to the subsequent symptoms varies greatly by species and tissue. Consequently, the protection provided by H1 antagonists varies correspondingly. Edema development and itching are successfully controlled in people. Other symptoms, like hypotension, are less well counteracted. This can be explained by the involvement of other subtypes of H receptors as well as the impact of other mast cell mediators, primarily eicosanoids. If at all, bronchoconstriction is only little lessened. We should remember the role of adrenaline in managing type I hypersensitivity reaction, anaphylaxis as it is the physiological antagonist of histamine

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CNS	First-generation AHs can both excite and depress the central nervous system. On occasion, people given typical dosages experience stimulation; they become restless, anxious, and unable to sleep. Overdose is also characterized by central excitement, which frequently culminates in convulsions, especially in newborns. On the other hand, older H1 antagonists typically cause central depression when administered at therapeutic levels. Common symptoms include reduced attentiveness, slower response times, and somnolence. Patients' sensitivity to and reactions to various medications vary. The ethanolamines (such as diphenhydramine) are likely to induce sedation. Due to the drowsiness caused by first-generation antihistamines, many patients cannot take or utilize these medications safely, except at evening. Patients may still have a "hangover" from antihistamines the next morning, resulting in drowsiness with or without psychomotor impairment. It is unknown if tolerance to such side effects develops with prolonged administration of split dosages to individuals with chronic urticarial disorders. Thus, the introduction of "nonsedating" AHs of the second generation was a significant step that enabled their widespread usage. These more recent H1 antagonists do not significantly pass the blood-brain barrier. Their sedative effects are comparable to placebo effects. Numerous antipsychotic drugs include H1 and H2 receptor antagonists; however, it is unknown whether this characteristic contributes to their antipsychotic effects. Clozapine, an atypical antipsychotic drug, is an efficient H1 antagonist, a mild H3 antagonist, and an H4 receptor agonist in rats. The weight gain impact of standard and atypical antipsychotics is caused by the H1 antagonist action of these medicines
Anticholinergic effects	Many of the first-generation AHs have the potential to suppress reactions to acetylcholine (Ach) that are mediated by muscarinic receptors in clinical settings. Some AHs are also effective in the treatment of motion sickness. Anticholinergic features of H1 antagonists may be substantially responsible for scopolamine's significant antiemetic action, since scopolamine effectively reduces motion sickness. In fact, among these drugs, promethazine has the most muscarinic-blocking action and is the most effective AH against motion sickness. The second-generation AHs have no impact on muscarinic receptors
Local anesthetic effects	A few AHs seem to be more potent than procaine in their local anesthetic effects. Promethazine is particularly effective. However, the doses necessary for this effect are far larger than those required to block the interactions between histamine and its receptors

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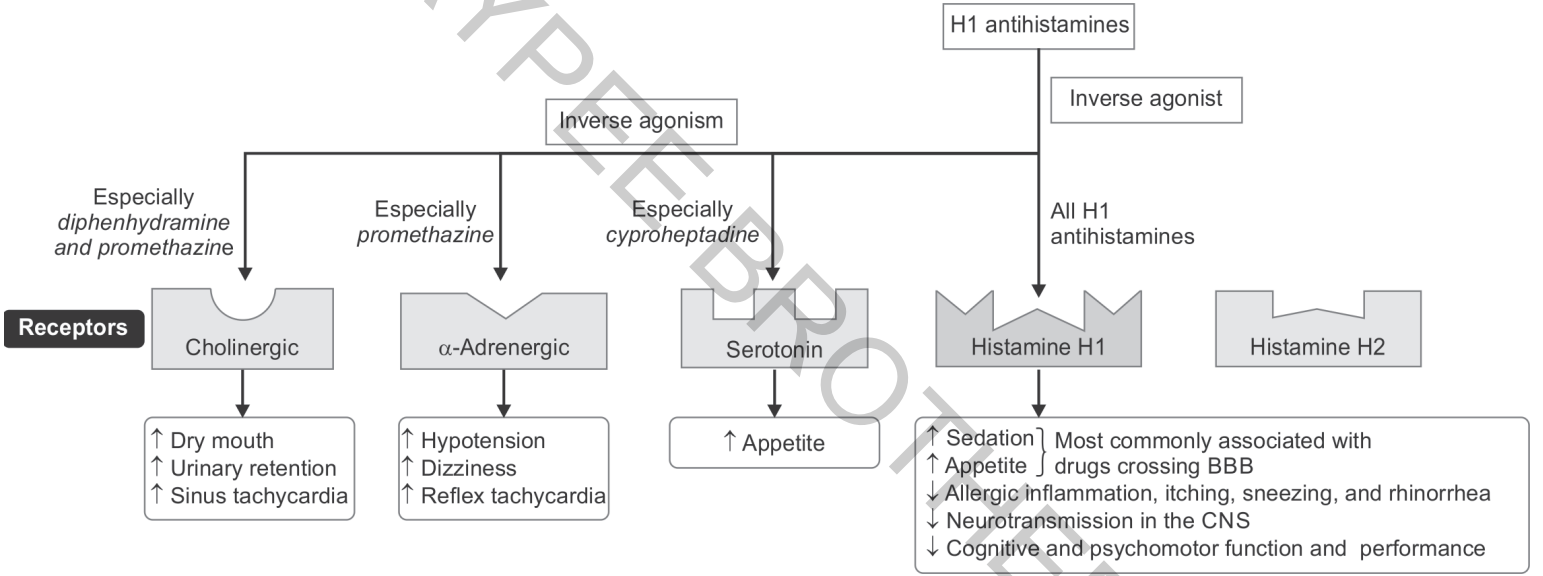

FIG. 1: Affinity of different antihistamines (AHs) with H1, H2, serotonin, alpha-adrenergic and cholinergic receptors.

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not improve the quality of sleep.[6,7] In addition to poor sleep pattern, older AHs are reported to cause poor school performances.[8] First-generation AHs have been associated with injuries and fatalities due to car, plane, and boating accidents.[9]

- *Toxicity*: Diphenhydramine and other first-generation AHs are documented drugs due to their abusive potential. Overdose is associated with anticholinergic effects including fever, flushing, pupillary dilatation, urinary retention, tachycardia, hypotension, and coma.[10] Accidental consumption in infants and children or overdosing leads to paradoxical excitation including irritability, hallucinations, and seizures followed by drowsiness, delirium, ultimately resulting into respiratory depression and coma.[10,11]
- *Risk of QT prolongation and torsade de pointes:* First-generation AH, such as hydroxyxine, can increase the risk of QT prolongation and torsade de pointes.[12,13]

As stated earlier, newer-generation medications have minimal serious safety concerns.[5] There have been no fatalities directly associated with the use of the newer-generation AHs available in the United States. Accidental exposures of up to 30-fold ingestions of cetirizine, loratadine, and fexofenadine have not resulted in any serious adverse events.[14,15] Two second-generation AHs (astemizole and terfenadine) have been associated with cardiac toxicity; however, both were removed from the market over 20 years ago.

PRESCRIBING ANTIHISTAMINES IN SPECIAL SITUATIONS

Antihistamine Prescribing in Renal Insufficiency

Among the newer-generation AHs, bilastine, ebastine, and fexofenadine can be used safely in patients with renal insufficiency. It is better to avoid desloratadine and levocetirizine in renal insufficiency. Dose modification requires while prescribing levocetirizine in renally compromised patients (contraindicated when eGFR is <10 mL/min).[16,17]

Prescribing Antihistamine in Liver Failure

The use of any antihistamine bears the risk of precipitating liver encephalopathy, in cases of serious liver failure. Dose adjustment is not required while prescribing bilastine, desloratadine, levocetirizine, and fexofenadine in patients with hepatic failure. The dose of ebastine should not exceed

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10 mg in patients with a compromised liver. However, the use of mizolastine is contraindicated in hepatic failure.[18]

Use of Antihistamines during Pregnancy

Antihistamines such as astemizole, terfenadine or fexofenadine and azelastine, levocabastine and olopatadine (for external use), are classified as class C according to the Food and Drug Administration (FDA) regulations, based on their teratogeny in animals. Cetirizine, loratadine, ebastine, levocetirizine, desloratadine, rupatadine, and bilastine are considered safe during pregnancy due to absence of teratogenicity in studies on animals.[19]

Use of Antihistamines in Geriatric Population

Prescribing AHs in geriatric population seeks special attention. Multiple comorbidities and polypharmacy are major causes contributing to the increased burden in anticholinergic score among geriatrics. First-generation AHs should be avoided in elderly population as these agents are associated with anticholinergic (aggravates urinary retention and decreased secretions), antiseronergic, antidopaminergic and high penetratability through blood-brain barrier producing adverse effects such as lack of coordination, alterations in memory, dyskinesia, anxiety, confusion, sedation, vertigo, somnolence, or the activation of epileptogenic foci. This group of AHs is also characterized by its anticholinergic, antiserotoninergic, and antidopaminergic activity, which could condition symptoms such as urine retention, arrhythmias, peripheral vasodilatation, postural hypotension, tachycardia, mydriasis, which can aggravate earlier pathologies in elderly patients.[20] Second-generation AHs are safe and are associated with lesser adverse effects these agents can be prescribed in elderly, with risk benefit analysis.

Use of Antihistamines in Children

There are limited studies on the safety profile of AHs in pediatric population. First-generation AHs have been little studied from the viewpoint of safety in children. There are multiple documented rare side effects in pediatric population who were put on first-generation AH therapy; these include alterations of vision, dryness in mucous membranes, and other effects arising from their anticholinergic action. The commonly prescribed AHs in pediatric population includes cetirizine, levocetirizine, loratadine, desloratadine, ebastine, and fexofenadine have been well documented for their safety in the short, medium,

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and some in the long-term.[21-26] It can be concluded that second-generation AHs with approved indications for their use in pediatric ages have their safety and effectiveness much better documented than first-generation AHs.

Use of Antihistamines in Breastfeeding

Transport of drugs to the maternal milk is greater when the drug is more lipid soluble. Ionization of basic drugs makes it more available in mother's milk. In a clinical study, the percentages of detection of loratadine/desloratadine and fexofenadine in mother's milk was found to be 1.1% and 0.45%, respectively; thus, there is minimal exposure of the breastfed baby in mothers who require these treatments.[27,28]

CONCLUSION

- First-generation AHs should be avoided as first-line treatment in allergic disease since they are associated with potential adverse effects, which may at times prove to be fatal.
- Fatal injuries can be prevented by avoiding first-generation AHs; it is a harsh truth that the level of CNS impairment is not fully appreciated by majority of prescribers.
- Prescribing AHs in geriatric population should be done after foreseeing the risk of anticholinergic burden, as obtained by Anticholinergic Burden Scale (ACB) score.
- Newer-generation AHs, unlike first-generation AH, are safer and have faster onset of action, also superior in potency, and efficacy.
- Further efforts are needed to disseminate this information to healthcare providers and patients to help change practice and improve patient health and safety.

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Jyotirmoy Pal MBBS MD (General Medicine) FRCP FICP FACP WHO Fellow is a Professor (General Medicine), College of Medicine, and Sagore Dutta Medical College, Kamarhati, West Bengal, India. He is the Dean of Indian College of Physician (ICP) and President-Elect of Association of Physician (API). His fields of interest are Infectious and Tropical Diseases and Geriatric Medical and Public Health. In the last 21 years, he has published more than 80 research articles in national and international indexed journals. He served as a secretary and an editor for the Journal of Indian Medical Association (JIMA). He contributed chapters in more than 30 books and is the Editor of Monograph Dengue, Clinical Methods in Respiratory Medicine, and Mucormycosis. He is also the Editor-in-Chief, MacMaster Textbook of Internal Medicine, South-Asian edition. He has been a member of the Expert Committee on COVID Care, Dengue Management, Department of Health and Family Welfare, Government of West Bengal.

Nandini Chatterjee MD FRCP(London Glasgow) FICP is working as a Professor, Department of Medicine at the Institute of Postgraduate Medical Education and Research (IPGMER) and SSKM Hospital, Kolkata, West Bengal, India. She has 20 years of teaching experience and her field of interest is Tropical Diseases. She has published over 70 research articles in different national and international indexed journals. She has previously served as an Editor for the Journal of the Indian Medical Association (JIMA) and presently serves as the Editor-in-Chief of the Bengal Physician Journal (Association of Physicians of India). She has been an invited author of different books—API Textbook of Medicine, Medicine Update, Eye in Systemic Diseases, 100 Best Cases in India, COVID 2nd Wave, etc. She is also the Editor of Mucormycosis and co-Editor-in-Chief of McMaster Textbook of Internal Medicine, South-Asian edition, Tropical Fever, and Dengue, 3rd edition.

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