Review article

Five decades of Antihistamines - an objective analysis

Balakrishnan D *

***Senior Assistant Professor of ENT, Madras Medical College and Civil Surgeon at the Peripheral Hospital, Chennai 600082 India.** **Adapted from a guest lecture delivered by the author at the Fifth National Conference of The Association of Paediatric Otolaryngologists of India 18-20 September 1998 Trivandrum, India. This is a review article, coloured with two decades of personal experience. Each statement in this article is substantiated by bibliography. The unwieldy list of references has been intentionally pruned in the interest of fluency and brevity.**

Preface

The antihistamine is a commonly used drug. The number of antihistamines is bewildering. This number keeps on increasing. Little distinction can be made between the different compounds on the basis of efficacy. They do vary somewhat, however, with respect to potency, dosage, relative incidence of side effects, and the type of preparations available. Naturally, a physician would desire to choose a preparation that will afford the greatest therapeutic success with minimal side effects. Unfortunately, none of the antihistamines meet these criteria. Additionally, individuals vary significantly, in their responses to antihistamines. This fact also adds to the physician's conundrum.

But fortunately, all the available H1 blockers can be conveniently classified into several classes. It would seem wise for the physician to get familiar with a few representative compounds from the different classes and to base his choice on this knowledge.

Introduction

In the latest issue of Current Index of Medical Specialities (CIMS, a common compendium of drugs in India), eighteen different generic antihistamines are listed. The number of trade formulations exceeds 120. Very frequently, new antihistamines are launched. Each company claims that theirs is the best. The usual refrain is an introduction of minor changes in the chemical structure with a claim for a new name. This article is an objective analysis of the newer antihistamines. I have tried to be very concise, without sacrificing information and fluency.

The hypersensitivity reaction

The most important player in the ‘allergy-reaction’ is the mast cell. First, the mast cells get sensitized to an antigen. On subsequent re-exposure, they degranulate and release histamine and similarly acting substances. This causes the typical reaction of itching, nasal stuffiness, watery eyes and nose, sneezing, bronchospasm etc. This occurs within the first several minutes and is aptly called the Early Phase Reaction. In approximately half the patients, a late phase reaction also occurs in the next 3-10 hours. This phase is characterised by an inflammatory infiltrate i.e. increased number of eosinophils, basophils and mast cells in the affected tissue. It is during this late phase that several other mediators like leukotrienes, prostaglandins and platelet activating factor are produced. The net interactive mediator effect is mucosal engorgement. Additional inflammatory response results in further symptoms. Patient remains hypersensitive to antigen exposure for several hours to several days. With repeated exposure, the late phase can become chronic.

Histamine inhibitors

In 1910, Dale and Laidlaw discovered histamine. After the discovery of histamine, thirty six long years had to be spent in painstaking research before a compound to block its action could be found. But this phenolic ether amine was never used in humans because it was too toxic. Another seven years had to pass before the first clinically useful anti histamine, Pyrilamine could be synthesized. Soon, several compounds made their appearance. They are now collectively called the first generation anti histamines. They were all lipid-soluble and consequently crossed the blood-brain barrier – resulting in sedation. Some have the unsavoury side effect of producing neural stimulation also, leading to tremulousness. Even convulsions can result with supra therapeutic doses. In the last 15 years, newer methods of synthesis led to the development of less lipophillic antihistamines. Consequently, they are less liable to reach the brain and thus less liable to produce sedation. These were called second generation antihistamines. Inspite of their side effects, several first generation antihistamines are still usefully employed for specific indications (Table1).

Clinical considerations

The Antihistamines are competitive inhibitors of histaminic action, either at the H1 or the H2 receptor sites. They prevent the action of histamines, rather than reverse it. Hence they are better given before histamine liberation occurs i.e. before the antigen challenge occurs. Despite claims to the contrary, as a class, they lead to some degree of dry mouth, sedation, lassitude and gastro intestinal symptoms. In a clinical situation when a patient presents to you with signs of severe allergy, the drug of choice is adrenaline a potent physiological antagonist of histamine. Further, several antihistamines do not block the production of late phase mediators. This is why sometimes we need drugs other than antihistamines like steroids (Table 2).

Properties of newer antihistamines

In table 3, the salient properties are indicated. Briefly put, all new antihistamines except cetirizine,are less sedating. Terfenadine has a potential to lead to cardiac arrhythmia. Loratidine can be given once a day. In view of the diurnal variation of the inhalational

allergy, this antihistamine can usefully be given in the night, so that it can cover the early morning period.

Table1. First generation Antihistamines still in use

Drug
Diphenhydramine
Cyclizine
Hydroxycine
Promethazine
Chlorcyclizine
Triplennamine

Table2. Drug therapy of allergy

Type of drug	Actions
Antihistamines	block histamine receptors
Steroids (systemic / nasal)	local anti inflammatory
Cromolyn sodium	stabilise mast cell membrane / prevent degranulation
Nasal decongestants (systemic/ nasal)	relieve nasal stuffiness
Immunotherapy	induces neutralising antibody (IgG)

Table3. Second generation Antihistamines which are commonly used

Drug	Actions of all the second gen drugs
Cetirizine	selective H_1receptor antagonist
Terfenadine	local anti inflammatory
Loratadine	stabilise mast cell membrane
Fexofenadine	prevent degranulation
Azelastine	