Effectiveness and safety of new-generation antihistamines in allergenic rhinitis and urticaria

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Abstract

Allergic diseases are on the increase, affecting 30-40% of the population. Histamine remains the most important mediator of clinical reactions in allergic diseases such as rhinitis, urticaria, and food and drug allergies.

The need for more effective and safe antihistamines is critical and intensive drug development has become more demanding and competitive.

Although the old "first generation" antihistamines were effective, major limitations included their strong potential for sedation and their anti-cholinergic side effects. Not only could patients not function well in their normal daily activities, but these medications posed an important risk for safety, particularly for motor vehicle drivers and machine and precision instrument operators. Unacceptable side effects were a particular problem in the elderly.

In May 2001, CONGA, an international consensus group, convened to formulate guidelines for the development of new antihistamines. Several important areas were reviewed and a document of recommendations was published, focusing specifically on the safety and efficacy aspects of antihistamines.[1] ***(SA Fam Pract 2004;47(1): 24-28)***

Introduction

The important new issues pertaining to antihistamines were identified as follows:

1. Anti-inflammatory properties
2. Potency, efficacy and effectiveness
3. Lack of cardiotoxicity
4. Drug-drug interactions
5. Lack of CNS interactions

In classifying the available antihistamines, the "first-generation" antihistamines were those that historically were the first on the market (e.g. chlorphenirimine, diphenhydramine, hydroxyzine). Many of these are still over-the-counter medications.

There are four major types of histamine receptors: H_1, H_2, H_3 and H_4. All are hepta-helical structures that transduce extracellular signals via G-proteins and all have constitutive activity, which is defined as the ability to trigger downstream events, even in the absence of ligand binding. The H_1 receptors are the most important in allergic rhinitis and in chronic urticaria. They have about 45% homology with muscarinic receptors, and this explains why some antihistamines induce anticholinergic side effects. Second-generation antihistamines are less lipophilic than some of the older, first-generation antihistamines, and do not cross the blood brain barrier.

Some of the second-generation antihistamines, like fexofenadine, are actively transported into the lumen of the gut, kidney and brain by p-glycoproteins, which restrict their ability to accumulate and cause unwanted side effects. However, agents such as rifampicin, which induce p glycoprotein, may increase the clearance of fexofenadine and reduce its efficacy.

The second-generation antihistamines were therefore developed as H_1 blockers, which have fewer unwanted side effects, particularly sedation. However, two of these, astemizole and terfenadine, have serious cardiac side effects, resulting in prolonged Q-T intervals and arrhythmias and were withdrawn from the market. Effective and safe second-generation antihistamines developed at this time include cetirizine and loratadine. Neither of these have significant cardiac side effects.

It is hoped that the development of a "third" generation of antihistamines, which act differently to current receptor antagonists and are devoid of all side effects, will soon be completed. These are not yet available commercially.

Recently, new formulations that are related to previous second-generation antihistamines have become available on the South African market. These include desloratadine, fexofenadine and levocetirizine, and are currently referred to as "new-generation" antihistamines.

The mechanism of histamine receptor antagonism has recently been carefully explored in vitro and in vivo, and it is now understood that the new-

generation antihistamines, such as levocetirizine, are actually "inverse agonists" rather than receptor antagonists, i.e. they do have intrinsic activity at the histamine receptor site, other than competing for histamine 1 binding.

Desirable properties of antihistamines

The desirable properties of antihistamines were clearly defined and summarised in the CONGA consensus document.[1]

a. Anti-inflammatory properties

It is well understood that chronic inflammation is an important part of the pathology of allergic rhinitis and asthma. There is strong experimental evidence in vitro that all the new-generation and second-generation antihistamines possess anti-inflammatory properties related to inverse agonist effects at the H_1 receptor site. These include effects on eosinophils,[2] adhesion molecules,[3] T-lymphocytes[4] and cytokines. In the nose, relief of nasal obstruction via such anti-inflammatory effects would be of important additional clinical benefit to blocking the effects of histamine. The relief of nasal obstruction by levocetirizine,[5] fexofenadine[6] and desloratadine shown in recent studies may be the result of these anti-inflammatory activities.

b. Potency, efficacy and effectiveness

New antihistamines need to be potent and specific for the H_1 receptor. It has been found that antihistamines with the highest affinity for the H_1 receptor may not be the most effective clinically.

It is interesting that, in general, first-generation antihistamines such as hydroxyzine and chlorpheniramine are more effective for the relief of itching in eczema than the new-generation, or second-generation, antihistamines. However, second-generation and new-generation antihistamines are highly effective for the relief of itching in urticaria and rhinitis. The onset of action is variable, but it is generally within 90 minutes for the new-generation antihistamines.

c. Lack of cardiotoxicity

Since the withdrawal of astemizole and terfenadine from the market, close surveillance of the potential cardiotoxicity of new antihistamines has been important. Adverse effects are consequent to the direct blockade of potassium channels, which control the repolarisation phase of the cardiac action potential.

No clinically significant cardiac effects have been reported for loratadine, fexofenadine, desloratadine, levocetirizine or cetirizine.

It is advisable, however, to be careful about using antihistamines in patients with pre-existent diseases of the conduction system of the heart, or patients with ischaemic heart disease or cardiomyopathy.

d. Lack of CNS effects

Subjective sleepiness is a well-known side effect of antihistamines. Some older-generation antihistamines are even marketed as over-the-counter sleeping pills. Drowsiness appears to be a more significant problem in older subjects and rarely a problem in young children. Recent studies have shown that important new-generation antihistamines, e.g. fexofenadine,[7] have no effect on cognition or psychomotor functions and thus no impairment of driver behaviour.

Lack of CNS penetration has also been confirmed for new-generation antihistamines, such as fexofenadine, by positron emission tomography (PET). A lack of CNS side effects is also important in very young children, who may be given antihistamines to prevent the development of asthma. Excellent tolerability and safety in this regard has been confirmed by the ETAC study for cetirizine, which is used in young children to prevent the development of asthma.[8]

e. Lack of drug interactions

Antihistamines that are metabolised via the P450 cytochromes (CYP) in the liver have a potential for side effects when taken in conjunction with macrolides such as erythromycin, or with ketoconazole. Antihistamines that displace active transport mechanisms (p-glycoprotein) may also influence drug absorption.

New classes of antihistamines

New classes of antihistamines are theoretically possible and would act by binding to histamine and competing with histamine for the H_1 receptors. Other possible mechanisms would be by influencing the synthesis or metabolism of histamine or possibly by down regulating the expression of histamine receptors. Such new compounds are being explored in drug development programmes. They have the potential to represent a "third-generation" antihistamine in the future.

Antihistamines in allergic rhinitis

Antihistamines remain the mainstay of the treatment of allergic rhinitis. On the basis of the international ARIA guidelines, allergic rhinitis should be classified as "intermittent" (symptoms for fewer than four days per week or fewer than four weeks per year) or "persistent" (more than four days per week or more than four weeks).[9,10] Mild allergic rhinitis does not interfere with normal daily activities, sport, leisure or sleep.

Antihistamines are thus recommended as the first line of treatment for mild or moderately severe allergic rhinitis. Intranasal steroids are recommended for more severe symptoms and when antihistamines fail to provide adequate relief of symptoms, e.g. when nasal obstruction is the dominant symptom. Anti-histamines are particularly effective for the relief of symptoms such as rhinorrhoea, sneezing and itching. Effective doses for adults are 10 mg cetirizine, 5 mg desloratadine, 5 mg levocetirizine, 10 mg loratadine, 120 mg fexofenadine, and 4 mg chlorpheniramine. Antihistamines have also been found to be effective if applied topically, e.g. levocabastine. ketotifen eye drops are particularly effective in relieving the itching and redness caused by allergic conjunctivitis.

Recent studies in South Africa have found that certain new-generation antihistamines, e.g. levocetirizine, can also significantly relieve nasal obstruction.[5]

A new and important outcome measure for antihistamines in rhinitis is quality of life. The new-generation antihistamines have a significant impact on improving quality of life.[11]

Because of the strong link between asthma and rhinitis, the beneficial effect of antihistamines on asthma symptoms and hospitalisation has been studied by Peters et al.[12] Regular antihistamine or nasal steroid treatment for rhinitis in patients with both asthma and rhinitis can significantly reduce hospital admissions to emergency rooms for asthma exacerbations.

Antihistamines in urticaria

Antihistamines are highly effective for and the mainstay of the treatment of acute and chronic urticaria. They are recommended for use as the first line of treatment, and adequate doses of antihistamines reduce the requirement for oral steroids in resistant cases of chronic urticaria.[13] Night-time sedation with hydroxyzine, combined with the day-time use of a non-sedating antihistamine such as cetirizine, fexofenadine, levocetirizine or desloratadine, is effective and safe for both adults and children.

In some adult cases, the usual dose of antihistamine can be doubled to achieve a better therapeutic effect, and doses of up to 240mg of fexofenadine may be helpful in resistant cases. Children usually respond well to the recommended doses.

A few patients will benefit from the addition of an H_2 antihistamine (e.g. cimetidine). Clearly, antihistamines will only provide symptom relief, and it is important in the management of such patients that a careful history be taken to identify the triggers and precipitants of exacerbations, particularly in the patients' dietary and medication history.

Non-sedating antihistamines effectively relieve the symptoms of urticaria, as well as the quality of life of these patients, and are safe for long-term use.

Conclusion

New-generation antihistamines are safe and are indicated for rhinitis and urticaria. In atopic dermatitis, the central sedating effect of the older-generation antihistamines appears to be more important and these provide better symptom control, although side effects are not uncommon and caution should be exerted, particularly in the elderly and patients doing precision work or driving vehicles.

Antihistamines are now also considered to be anti-inflammatory and, although far less potent than glucocorticosteroids as anti-inflammatory agents, the beneficial anti-allergic effects related to their inverse agonist anti-inflammatory effects are increasingly being appreciated.

See CPD Questionnaire, page 30

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