

Original article

Antihistamines: do they work? Further well-controlled trials involving larger samples are needed

Histamine is one of the most important steps in the phlogistic allergic reaction. Its activity is due to the link to specific receptors on the cellular surface. H1-receptors of second generation are the most currently prescribed drugs in allergic diseases for their high selectivity, little or no central sedative effect, rapid onset of action and long half lives. Antihistamines can modulate part of immunological mechanisms involved in the pathogenesis of allergic inflammation reducing mediator release and expression of adhesion molecules, regulating the release of cytokines, chemokines and consequently inflammatory cells recruitment. The anti-inflammatory effects of cetirizine, desloratadine and levocetirizine are reviewed. Quality of life is considered too, as a main parameter in a global evaluation of the antihistamine's effects.

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Histamine is one of the most important phlogistic mediators of early-phase allergic immunoglobulin E (IgE) -mediated reactions in atopic disease. Several studies have demonstrated that the last steps of allergic reactions are mediated through the histamine bond to distinguish histamine receptors (H1, H2, H3, H4 receptors) which are set on the cellular surfaces of almost every tissue. A different physiological effect will occur in accordance with the type of receptor stimulated by histamine. In bronchial asthma, pathophysiological events deriving from H1-receptor stimulation cause phenomena such as bronchial smooth muscle contraction, hypersecretion and thickening of mucus bronchial wall oedema caused by the increasing vascular permeability and vasodilatation. The last two mechanisms are also responsible for other allergic disorders such as rhinoconjunctivitis (nasal obstruction, runny nose) and urticaria (skin wheals) (1). Acting on the same receptor, histamine is also the mediator of skin itch, although recent studies have revealed that mediators different from histamine are involved in the induction of pruritus. Among these are mast cell tryptase (which acts on proteinase-activated receptor 2 in sensory nerves) and substance P (2). In the cardiovascular system, histamine induces vasodilatation and blood pressure reduction and also has H2- and H3-receptor-mediated positive inotropy and bathmotropy effects. Histamine inhibits interleukin-12 (IL-12) and tumour necrosis factor- α (TNF- α) and

increases IL-10 release from dendritic cells and monocytes activating H2 and H3 receptors. In this way dendritic cells induce T helper type 2 differentiation and thus the allergic reaction (3). The H4 receptor can modulate immune cell functions and recent Northern blot analysis studies have shown its expression on mast cells and eosinophils. H4-receptor activation seems to be important for chemotaxis and the accumulation of cells in inflamed allergic tissue (4,5). Antihistamines that block the H1 receptor are very important to the management of allergic disease. They can be classified in three groups: first-generation antihistamines (promethazine, hydroxyzine, chlorpheniramine, deschlorpheniramine, ketotifen, oxatomide, cyproheptadine), second-generation antihistamines (cetirizine, loratadine, mizolastine, ebastine, terfenadine) and new-generation antihistamines (fexofenadine, levocetirizine, desloratadine). Unlike highly selective second- and third-generation drugs, the first-generation antihistamines display poor selectivity for the H1 receptor and have few or no central nervous system sedative effects, a rapid onset of action and long half-lives (6). It is for these features that they are the most currently prescribed antihistamines. Indeed, they relieve symptoms such as nasal congestion, rhinorrhoea, sneezing, itching and skin wheals. Nevertheless, several studies have demonstrated that H1-antihistamines are not just symptomatic drugs, but also have important anti-inflammatory effects.

Anti-inflammatory effects of antihistamines

Antihistamines can modulate those parts of immunological mechanisms involved in the pathogenesis of allergic inflammation by reducing mediator release and the expression of adhesion molecules, by regulating the release of cytokines and chemokines (7), and consequently inflammatory cell recruitment. The antiallergic properties of antihistamines refer to their ability to inhibit histamine production and release by basophils, by reducing the synthesis and release of arachidonic acid metabolites and down-regulating intercellular adhesion molecule (ICAM-1) expression on epithelial cells and fibroblasts at the inflammation site (8). They can also interfere in eosinophil functions by inhibiting chemotaxis and survival. Release of inflammatory cytokines such as TNF- α , IL-1 β and IL-6 can be reduced as both *in vivo* and *in vitro* studies of antihistamine treatment have demonstrated (9). Moreover, other cytokines with immunoregulatory functions, in particular IL-4 and IL-13, are seen to be decreased with H1 antagonists (10). These anti-inflammatory properties of the second- and third-generation antihistamines have been extensively studied *in vitro* with drug concentrations higher than *in vivo*. However, these activities have also been demonstrated *in vivo* at therapeutic dosages. The antiallergic action of first-generation antihistamines has long been known also to inhibit allergen-induced histamine release from human basophils (11). Antihistamines remain the drugs of first choice in the treatment of allergic diseases such as rhinoconjunctivitis and urticaria, and their usefulness in bronchial asthma and atopic dermatitis is still being investigated; however, their immunoregulatory activity gives them a potentially fundamental therapeutic role in many more conditions than mere symptomatic relief.

Cetirizine

The effects of cetirizine are the result of selectivity to H1 receptors and anti-inflammatory activities. It has been shown that cetirizine can, *in vitro*, reduce ICAM-1 expression on mucosal epithelial cells and fibroblasts and the survival and chemotaxis of eosinophils are inhibited in the nose, conjunctiva, lung mucosa and in the skin (12,13). Studies conducted *in vivo* confirmed the activity of cetirizine in down-regulating ICAM-1 expression and allergic cell infiltration in the conjunctival epithelium (14).

The role of cetirizine, and of antihistamines in general, similarly to the symptomatic treatment of asthma, seems to be of little relevance if compared with corticosteroids and β_2 -agonists. However, a major study carried out to evaluate the power of cetirizine to prevent or delay bronchial asthma in children with atopic dermatitis has shown that asthmatic symptoms can be prevented in aeroallergen-sensitized children during cetirizine

treatment and, furthermore, that it delays the onset of wheezing after treatment discontinuation (15). As a result of the lack of effect of other antihistamines, cetirizine has been used in two cases of acquired cold urticaria in association with zafirlukast with positive results confirmed by an improvement of the ice-cube test reactivity and by the patient's self-evaluation (16). The Early Prevention of Asthma in Atopic Children study (EPAAC) was carried out to confirm the findings of the Early Treatment of the Atopic Child study (ETAC) and to investigate if asthma can be delayed by levocetirizine in children with atopic dermatitis sensitized to specific aeroallergens. Ketotifen revealed the same capacity to prevent asthmatic symptoms in children with atopic dermatitis and elevated total IgE levels but not in those with normal total IgE (17).

Desloratadine

Desloratadine is the primary metabolite of loratadine with selective H1-receptor antagonist activity.

The anti-inflammatory properties of desloratadine that have been reported consist of the inhibition of the release of pro-inflammatory cytokines such as IL-4 and IL-13 (which are both involved in IgE-mediated and non-IgE-mediated histamine release by basophils), IL-6, IL-8 and histamine release from basophils and mast cells (18). Moreover, at higher dosages it reduces prostaglandin D2 (PGD₂), leukotriene C₄, and tryptase synthesis from human basophils via the Fc ϵ RI system (19). It has been shown that desloratadine can reduce ICAM-1 expression on nasal epithelial cells with consequent inhibition of allergic cells (20). Many clinical trials have been conducted to evaluate the efficacy of desloratadine in the treatment of seasonal allergic rhinitis. In two randomized, double-blind, placebo-controlled studies, the efficacy evaluation was obtained through a twice daily total symptom score assessment (TSS: the patient referred the intensity of nasal and non-nasal symptoms using a four-degree scale), in the morning – just before drug administration – and 12 h later. In the first study of 346 patients, those who received desloratadine showed a statistically significant reduction in symptom score (28%) from baseline compared to a placebo group. This reduction was obtained on the second day of treatment and lasted throughout the treatment period. The second study ($n = 328$ patients) confirmed these results and described a 30% reduction of TSS in the active treatment group compared to the placebo group (21). A placebo-controlled trial has also investigated the efficacy of desloratadine in 676 patients with perennial allergic rhinitis: a significant reduction in TSS was shown in a comparison with the placebo group, further reporting a fast onset of action from the first assessment of TSS (22). Baena-Cagnani described a significant reduction in total asthma symptom score in patients with seasonal allergic rhinitis and concomitant asthma (23). Several trials have

evaluated the efficacy of desloratadine in patients who showed chronic idiopathic urticaria. A double-blind, placebo-controlled study of 190 patients with moderate-to-severe urticaria demonstrated that desloratadine is a safe and effective treatment with rapid onset of action, providing long-term symptomatic relief. These effects are the result not only of its antagonist activity towards H1 receptors, but also of its inhibitory effects on inflammatory mediators (24).

Levocetirizine

Levocetirizine is the active, levorotatory enantiomer of cetirizine with a major antihistaminic activity capable of inhibiting the histamine-induced wheal and flare reaction in the skin better than ebastine, fexofenadine, or mizolastine (25). Moreover, *in vitro* studies described the capacity to reduce IL-5-induced eosinophil chemotaxis with a consequent decrease of allergic cell recruitment at the inflammatory site (26). The clinical efficacy of levocetirizine was compared with loratadine in a double-blind, placebo-controlled crossover study and 83.8% of patients who received levocetirizine described a significant improvement in symptom score vs 66.7% of patients receiving loratadine (27).

Quality of life

In current medical research and practice the effect of a treatment is measured not only on the basis of clinical indices but also by considering health-related quality of life (HRQoL) endpoints. This approach allows the integration of traditional parameters with a validated and standardized assessment of the patient's viewpoint about the treatment impact on daily life and well-being (28). In testimony of the interest raised by this topic, a literature search focusing on HRQoL and antihistamines in allergic diseases retrieved 108 studies between 1983 and 2003. Most of them (84) regard the subjective impact of anti-H1 treatment in patients with respiratory allergy; 15 assess HRQoL in clinical trials involving patients treated for skin diseases, and seven are about

allergic diseases in general. Several studies have demonstrated that antihistamines have a statistically significant effect on the HRQoL of allergic patients. Murray et al. (29) evaluated the HRQoL impact of treatment with cetirizine in seasonal allergic rhinitis in a randomized double-blind, placebo-controlled trial over 3 weeks by means of a specific instrument, the Rhinitis Quality of Life Questionnaire (RQLQ). Actively treated patients, in opposition to a placebo-treated group, have a significant improvement in HRQoL scores (RQLQ total score and in each of the seven domains) at weeks 1, 2 and at the end of the study. Thompson et al. (30), in a double-blind, placebo-controlled study, assessed the effect of fexofenadine on HRQoL and working capacity of patients with chronic urticaria by using two validated instruments: the Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment instrument. The study demonstrated that, compared with placebo, fexofenadine significantly improves quality of life ($P < 0.0002$), productivity at work ($P = 0.0012$) and daily activities ($P = 0.0002$). HRQoL data are also used to compare the effect of different antihistamines on patients' well-being. Thus Harvey et al. (31), in a prospective, two-phase, randomized single-blind clinical trial evaluated HRQoL related to treatment for SAR by comparing cetirizine, clorpheniramine and terfenadine treatments. The HRQoL score improved most after treatment with cetirizine and least after terfenadine. The results of this trial suggest that HRQoL data can be useful in the selection of an antihistamine treatment for SAR. Other studies include an assessment of HRQoL for a global evaluation of the effect of concomitant treatment for allergic diseases. For example, Meltzer et al. (32), in a multicentre DBPC 2-week trial, showed that montelukast and loratadine taken concomitantly, provided a significant improvement both in symptom score and HRQoL data, compared with placebo and each agent alone.

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