

EDITORIAL

Antihistamines as anti-inflammatory agents

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Histamine is an important chemical mediator of inflammation in allergic rhinitis, cutaneous allergic reactions and asthma. In the airways, it induces vasodilation of the post-capillary venules, with extravasation of fluid, protein and cells leading to mucosal oedema. It produces bronchoconstriction by direct stimulation of H1 receptors on smooth muscle and by indirect stimulation of parasympathetic reflexes. Airway hyper-responsiveness to histamine is a hallmark of asthma, and histamine is released from the airway mast cell granules. Increased plasma concentrations of histamine have been detected during both the early- and late-phase reactions following bronchial allergen challenge [1]. The level of histamine in bronchoalveolar lavage fluid from asthmatics has been found to correlate with airway hyper-reactivity and with asthma severity [2]. Histamine also has significant immune pro-inflammatory properties mediated by numerous cell types, including T cells, epithelial and endothelial cells and dendritic cells. For example, histamine can induce the expression of adhesion molecules on endothelial cells, such as E-selectin or ICAM-1 [3], trigger the production of IL-6 and IL-8 by endothelial cells [4] and up-regulate costimulatory molecules on dendritic cells [5]. Because histamine influences cell types that govern immune and inflammatory reactions, the therapeutic potential of H1-antihistamines in asthma has generated a great deal of interest. H1-antihistamines have been widely and successfully used in the treatment of allergic rhinitis and urticaria; however, their possible use in the treatment of asthma has been a matter of debate for about 20 years. The first-generation H1-antihistamines (i.e. chlorpheniramine, mequitazine, promethazine, etc.) have marked sedative effects, due to blood–brain barrier crossing. The so-called second-generation antihistamines (i.e. loratadine, cetirizine, terfenadine, ebastine, etc.) were engineered to be highly selective for the H1 receptor and are characterized by minimal sedative effects, rapid onset of action and long half-life. However, they still have dose-related adverse effects at high doses, in particular, sedative and anticholinergic effects. To address these therapeutic issues, third-generation antihistamines have been recently developed, which are either active metabolites (i.e. desloratadine, fexofenadine) or enantiomers (levocetirizine) of second-generation compounds. They exhibit more potent H1-receptor antagonist and anti-inflammatory activity than their parent compounds.

The anti-allergic properties of antihistamines usually refer to their ability to inhibit mast cell and basophil activity linked to the early-phase reaction. Such activity includes the inhibition of classical preformed mediators, such as histamine and tryptase, and has been demonstrated for available antihistamines [6–9]. More recently, desloratadine was demonstrated to inhibit basophil cytokines such as IL-4 and

IL-13 [10]. The importance of these cytokines in B cell activation and IgE synthesis would predict an interesting effect on IgE-mediated allergic reactions. The late-phase reaction is characterized by chemotaxis of inflammatory cells, including eosinophils and Th2 cells through the endothelial cell layer, followed by activation, differentiation and release of various mediators. New-generation antihistamines have shown inhibitory effects on the expression of adhesion molecules such as ICAM-1 on epithelial cells [11, 12] and P-selectin on endothelial cells [13], on eosinophil chemotaxis and activation both *in vitro* [14–17] and *in vivo* [18, 19], on inflammatory cytokine production such as IL-6 or GM-CSF [13, 20] and on chemokine release such as IL-8, RANTES and eotaxin [13, 17, 21, 22]. In addition, all the H1-antihistamines tested to date inhibit the constitutive H1-receptor-mediated NF- κ B transcription factor activation [23, 24], probably explaining their effects on cytokine production.

Few studies have evaluated the effects of antihistamines on Th2 lymphocytes, cells believed to orchestrate the allergic reaction [25, 26]. In these studies, terfenadine and desloratadine were found to inhibit Th2 cytokine production by peripheral blood T cells. In this issue of the journal, Nori et al. [27] have evaluated the effect of the second-generation H1-antihistamine ebastine on the production of Th2-type cytokines. Using T cells derived from healthy non-atopic volunteers, they showed that ebastine inhibited the secretion *in vitro* of IL-4 and IL-5, but not IL-2 and IFN- γ . This effect was not observed with the first-generation antihistamine ketotifen. Furthermore, there was also an inhibitory effect on T cell proliferation and macrophage-derived pro-inflammatory cytokines such as IL-6 and TNF- α . However, these data were obtained with cells from non-atopic donors stimulated with non-specific stimuli. Furthermore, these effects were observed with high concentrations of ebastine that would be achieved *in vivo* only with doses administered at several times the therapeutic dose. It would be interesting to assess the effect of H1-antihistamines on allergen-stimulated cells derived from allergic patients. Future work might also evaluate the effect on the cytokine profile of the allergic reaction of ebastine administered orally to allergic patients at therapeutic doses.

The clinical efficacy of second-generation H1-antihistamines in allergic rhinitis is well documented [28]. In asthma, the clinical evaluation of these new H1-antihistamines has been generally disappointing (for review see [29–31]). A meta-analysis of 19 double-blind, randomized, placebo-controlled studies of antihistamine in persistent asthma showed that the beneficial effects were outweighed by adverse effects [32]. However, some studies have reported beneficial effects. The first evidence for a potential benefit of new-generation

antihistamines was reported by Wood-Baker and Holgate [33] in 1993, who demonstrated a significant, but small, increase in the baseline FEV₁; however, none of these drugs could modify bronchial hyper-responsiveness (BHR) to methacholine as compared with placebo. Since then, many studies have evaluated new H1-antihistamines in asthma. According to the parameter assessed (symptoms, pulmonary function tests, bronchial reactivity and rescue medication use), the drug and the dose used, the results are very different from one study to another showing beneficial effects, mainly for asthma symptoms [34–38], sometimes for FEV₁ [39] and specific or nonspecific bronchial challenges [40–42, 32]. The general consensus for the currently used second-generation H1-antihistamines is that they lack efficacy at the standard doses used for allergic rhinitis. Higher doses may have modest effects, but at the expense of unacceptable side-effects [29–31, 43, 44]. It is unclear whether the differential effects observed in asthma and rhinitis are mediated by a different receptor or whether H1 receptors on different and activated inflammatory cell types are configured so as to require higher concentrations of the H1 antagonists for inhibition in asthma.

However, it should be stressed that some studies of patients with both rhinitis and asthma have demonstrated that control of upper airway symptoms with antihistamines can significantly improve asthma control [45, 46]. New molecules derived from pre-existing second-generation antihistamines have recently appeared on the market. Although few studies have been published on their potential activity in asthma, this early work appears promising. In particular, three recently developed molecules have all been shown to improve airway hyper-responsiveness and small airway calibre significantly [47].

Another consideration is the potential prophylactic role of H1-antihistamines in the development of asthma. Indeed, rhinitis seems to be a risk factor for developing asthma [48]. The link between rhinitis and asthma is not clear; however, specific allergen immunotherapy in patients with allergic rhinitis has been shown to decrease the development of asthma [49]. Thus, taking advantage of the anti-allergic activity of antihistamines, an indirect role in preventing asthma may be envisaged. One such study performed in children has shown that antihistamines could prevent the development of asthma in atopic children [50]. Another study has shown that in subjects with allergic rhinitis and no clinical asthma, antihistamines could decrease bronchial hyper-reactivity to metacholine after nasal allergen challenge [51].

In conclusion, the effect of currently available H1-antihistamines as symptomatic treatment in asthma seems to be of little help, although more studies are needed to evaluate their potential protective effect in the development of asthma. New molecules deriving from second-generation antihistamines might be more effective although, there too, more studies are needed.

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