

Anti-allergic properties of antihistamines in humans

R.J. DAVIES, J.L. DEVALIA

SUMMARY

The recent finding that an antihistamine administered regularly to 1-2 years old children with atopic dermatitis, prevented the subsequent development of asthma in those allergic to grass pollen or house dust mite has focused attention on the properties of this class of therapeutic agents. Is this effect simply due to antagonism of histamine, which may have wider actions in the development of airway inflammation than previously suspected, or is it a result of the anti-allergic properties exhibited by the second generation antihistamines? There are now many *in vivo* studies which have demonstrated that antihistamines decrease mast/basophil cell mediator release, inflammatory cell infiltration in allergic disease, and expression of adhesion molecules on epithelial cells. Numerous *in vitro* studies support these findings, extending the anti-inflammatory properties of antihistamines to decreasing eosinophil migration and release of pro-inflammatory mediators. We have established primary cultures of epithelial cells from nasal biopsies from seasonal allergic rhinitis outside the pollen season, and studied the effect of 0 to 10^{-3} M fexofenadine, the main active metabolite of terfenadine, on activated eosinophil-induced changes in electrical resistance (a measure of permeability of epithelial cultures) and release of pro-inflammatory cytokines and adhesion molecules. 10^{-9} to 10^{-3} M fexofenadine significantly inhibited eosinophil-induced increases in the permeability of the epithelial cell cultures and the release of IL-8, GM-CSF and sICAM-1. In addition, 10^{-6} to 10^{-3} M fexofenadine significantly inhibited cytokine-induced eosinophil chemotaxis and adhesion of these cells to endothelial cells.

KEY-WORDS: Antihistamines. – Anti-allergic compounds. – Epithelial cells. – Pro-inflammatory cytokines. – Adhesion molecules.

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RÉSUMÉ

Propriétés anti-allergiques des anti-histaminiques chez l'homme. – Il a été récemment montré que l'administration régulière d'un antihistaminique à un enfant de 1 à 2 ans atteint de dermatite atopique prévenait l'apparition ultérieure d'un asthme chez ceux qui étaient allergiques au pollen de graminée ou à l'acarien domestique, d'où un regain d'intérêt pour les propriétés de cette classe d'agent thérapeutique. Cela relève-t-il seulement de l'effet antagoniste sur l'histamine qui pourrait avoir, sur le développement de l'inflammation des voies respiratoires une action plus importante qu'on ne l'avait jusqu'ici soupçonnée ou est-ce le résultat des propriétés allergiques manifestées par les antihistaminiques de seconde génération ? Il y a maintenant de nombreuses études *in vivo* qui ont démontré que les antihistaminiques diminuent la libération de médiateurs par les mastocytes et basophiles ainsi que l'infiltration cellulaire inflammatoire dans les maladies allergiques et l'expression des molécules d'adhérence sur les cellules épithéliales. De multiples études *in vitro* confirment ces constatations, étendant les propriétés anti-inflammatoires des antihistaminiques à la diminution de la migration des éosinophiles et à la libération des médiateurs pro-inflammatoires. Nous avons d'abord mis en culture des cellules épithéliales provenant de biopsies nasales en dehors de la saison pollinique, chez des patients atteints de rhinite allergique saisonnière ; puis étudié l'effet de 0 à 10^{-3} M fexofénadine (principal métabolite actif de la terféfenadine) sur les changements de la résistance électrique induits par les éosinophiles activés (par mesure de la perméabilité des cultures épithéliales) et le largage de cytokines pro-inflammatoires et de molécules d'adhérence. La fexofénadine (10^{-9} à 10^{-3} M) inhibait de façon significative l'augmentation induite par les éosinophiles de la perméabilité des cultures de cellules épithéliales ainsi que la libération d'IL-8, de GM-CSF et de sICAM-I. De plus, la fexofénadine (10^{-6} à 10^{-3}) inhibait significativement le chimiotactisme des éosinophiles induits par les cytokines et l'adhérence de ces cellules aux cellules endothéliales.

MOTS-CLÉS: Antihistaminiques. – Cellules épithéliales. – Cytokines pro-inflammatoires. – Molécules d'adhérence.

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There is increasing evidence that histamine, a primary amine synthesised predominantly in mast cells and basophils, plays a key role in the pathogenesis of allergic airway diseases, including asthma and rhinitis [1]. Some studies have demonstrated that histamine levels in bronchoalveolar lavage (BAL) of symptomatic asthmatics are significantly increased, compared with levels in BAL of asymptomatic asthmatics, and may be increased by allergen challenge. Similarly, studies of allergic rhinitis have demonstrated that allergen challenge increased the levels of histamine in nasal secretions of these individuals.

Several studies have demonstrated that histamine contributes to bronchial obstruction in asthma, and to nasal blockage, sneezing and rhinorrhoea in rhinitis. At the cellular level, histamine causes smooth muscle contraction, increased vascular permeability and mucus secretion and parasympathetic nerve stimulation [2, 3]. It may also act on inflammatory cells and lead to release of mediators, such as leukotrienes and cytokines, and increased expression of class II antigens (HLA-DR) and ICAM-1 on epithelial cells [4, 5].

Despite the widely implicated role of histamine in the pathophysiology of allergic airway disease, antihistamines have been considered to be of little value in the treatment of asthma, and have generally been used in the treatment of allergic rhinitis, mainly for their symptomatic relief. More recently, several studies have demonstrated that some of the non-sedating second-generation H_1 receptor antagonists also possess anti-inflammatory properties, suggesting that these may potentially be useful in the management of airway inflammation in allergic airway disease. Most importantly, the recent double-blind randomised, placebo-controlled trial of cetirizine in 817 infants aged 1-2 years, with atopic dermatitis and a history of atopic disease in a parent or sibling (ETAC study), is of special interest. Cetirizine halved the number of children developing asthma in the subgroups sensitized to pollen or house dust mite [6]. Similar prevention studies with other antihistamines are in progress. Is this effect of the antihistamine cetirizine simply due to the H_1 receptor antagonism or a result of other anti-inflammatory effects of this class of drugs on a wide range of cells, particularly the eosinophil and the epithelial cell, and their protective effect on the barrier function of the airway epithelium?

Greiff and colleagues have investigated the effect of treatment with 20 mg loratadine od for 5 days on allergen-induced changes in the levels of nasal mast cell tryptase and α_2 -macroglobulin

in allergic rhinitis and demonstrated that release of both these proteins was significantly decreased after treatment with loratadine, compared with matched placebo [7]. The differences in release of α_2 -macroglobulin suggest that this drug may modulate the permeability of the microvasculature in the nasal airways. More recently, Ciprandi and co-workers have investigated the effect of topical azelastine [8] and oral terfenadine [9] on specific allergen (*Parietaria judaica*)-induced changes in the nasal airways of seasonal allergic rhinitis and demonstrated that these agents significantly decreased the airway inflammatory cell infiltrate and ECP levels in serum or nasal lavage of these individuals.

Several *in vitro* studies have also confirmed the anti-inflammatory properties of antihistamines. De Vos and co-workers have demonstrated that cetirizine can abrogate platelet activating factor (PAF) and N-formyl-met-leu-phe (FMLP)-induced chemotaxis of eosinophils *in vitro* [10]. Similarly, Kyan-Aung and co-workers have demonstrated that pre-incubation of eosinophils with 100 μ g/ml cetirizine significantly attenuated the ability of these cells to adhere to endothelial cells [11]. Eda and colleagues have demonstrated that loratadine can also attenuate PAF-induced eosinophil chemotaxis and O_2^- generation [12]. Lippert and colleagues have investigated the effects of loratadine on phorbol myristate acetate (PMA) and Ca-ionophore-stimulated release of cytokines from human mast and basophilic cell lines and demonstrated that loratadine significantly inhibited the release of IL-6 and IL-8 from these cells in a dose-dependent manner at all concentrations between 10^{-5} M to 10^{-14} M [13]. Other studies of human leucocytes have also demonstrated that loratadine can inhibit release of LTC_4 from stimulated basophil-enriched mononuclear cell suspensions. Recently, Genovese and colleagues have demonstrated that pre-incubation of purified basophils with either loratadine or DCL inhibited *Der p1* antigen or anti-Fc ϵ RI-induced release of histamine and LTC_4 [14]. Additionally, these authors found that both drugs led to a significant inhibition in the release of histamine, LTC_4 , PGD_2 and tryptase from purified human lung and skin mast cells immunologically challenged with anti-Fc ϵ RI.

Recent evidence suggests that antihistamines may also modulate airway inflammation by influencing the activity of the airway epithelial cells, which are thought to play an important role in the aetiology of allergic airway disease. Several studies have suggested that in addition to provi-

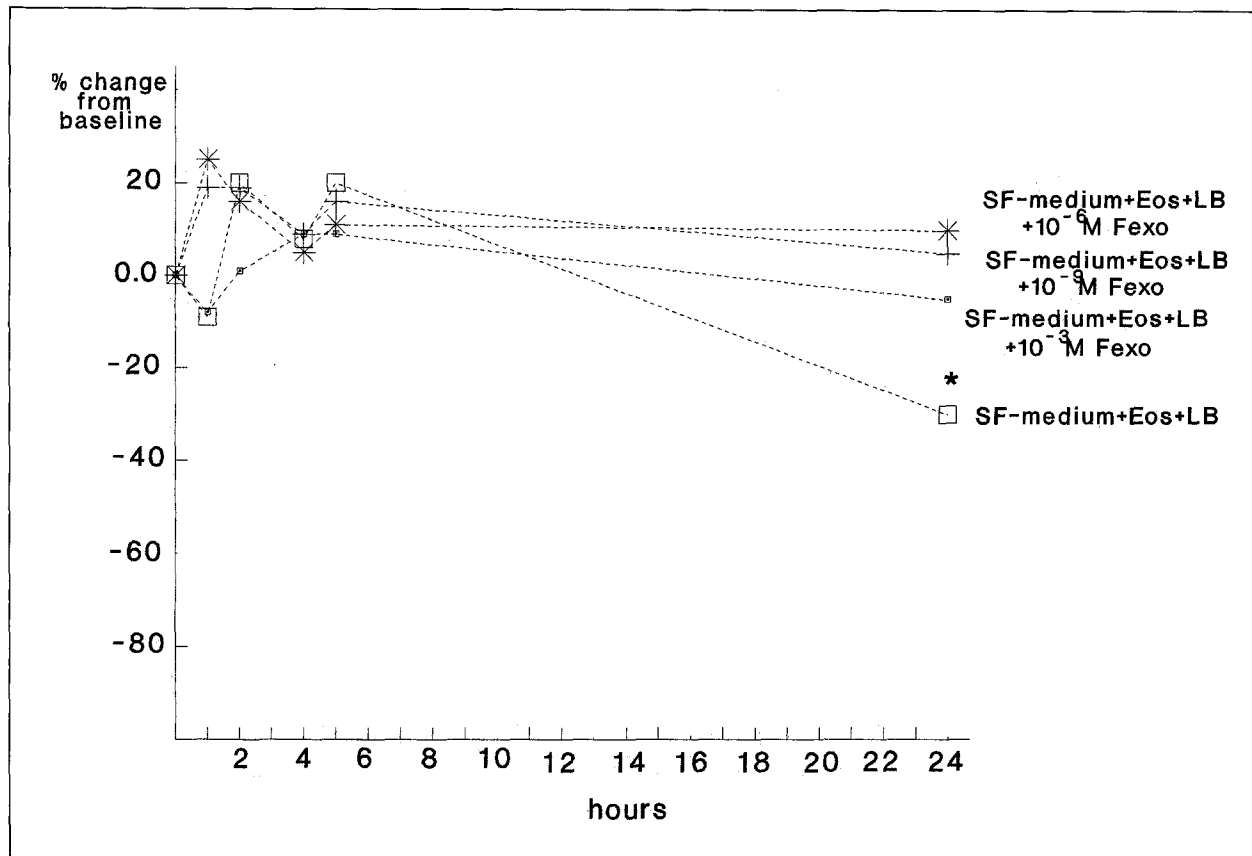


Fig. 1. – The effect of 10^{-9} – 10^{-3} M fexofenadine on activated eosinophil-induced changes in electrical resistance of HNEC cultures established from seasonal allergic rhinitics outside the pollen season. Results are expressed as percent change in electrical resistance from base line (SF-medium : serum free medium, Fexo : fexofenadine, Eos : eosinophils and LB : latex beads ; $n = 6$ for each set of experiments ; * $p < 0.05$ for cultures treated with eosinophils + latex beads vs cultures treated with eosinophils + latex beads in the presence of 10^{-9} – 10^{-3} M fexofenadine) (modified from Abdelaziz M.M. *et al.*, 1998).

ding a natural self-cleansing barrier against inhaled bacteria, particulates and allergens, the epithelial cells synthesise and release a large variety of inflammatory cytokines and adhesion molecules (including IL-1 β , IL-6, IL-8, IL-16, GM-CSF, MCP-1, RANTES, TNF α and ICAM-1), which influence the activity of eosinophils, mast cells, macrophages and lymphocytes, thought to play important roles in the allergic reaction [15]. Ciprandi and co-workers have investigated the effect of topical azelastine [8] and oral terfenadine [9] on (*Parietaria judaica*)-induced changes in expression of ICAM-1 in the nasal airways of seasonal allergic rhinitics and demonstrated that these agents significantly decreased ICAM-1 expression on nasal epithelial cells of these individuals. More recently, these authors have also demonstrated that treatment with 10 mg/day loratadine for 2 weeks, during the pollen season, significantly reduced the expression of ICAM-1 on

the nasal epithelial cells of seasonal allergic rhinitics [16].

In vitro studies with BEAS-2B cells, a human bronchial epithelial cell line, have demonstrated that diphenhydramine blocked histamine-induced increase in intracellular calcium [17]. Similarly, Vignola and colleagues have demonstrated that both pyrilamine (a H_1 -receptor antagonist) and ranitidine (a H_2 -receptor antagonist) inhibited histamine-induced increase in the expression of ICAM-1 and HLA-DR and release of fibronectin from bronchial epithelial cells [4]. More recently, these authors have demonstrated that loratadine and its metabolite descarboethoxylopratadine (DCL) significantly decreased histamine-induced expression of ICAM-1 on nasal epithelial cells *in vitro* [18].

We have recently cultured nasal epithelial cells (NEC) from biopsies of seasonal allergic rhinitics outside the pollen season and studied the effect

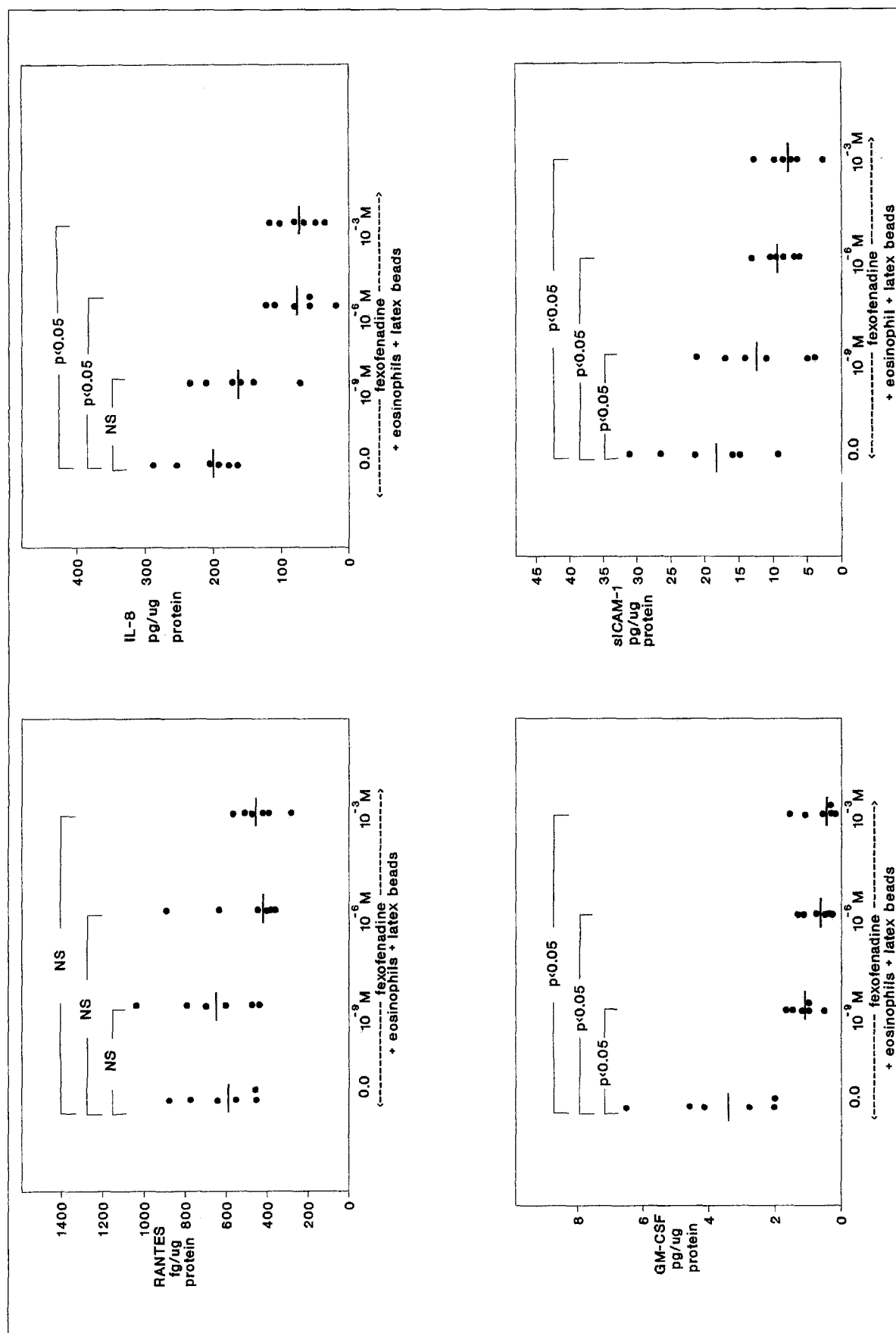


Fig. 2. - The effect of 10^{-9} - 10^{-3} M fexofenadine on activated eosinophil-induced release of RANTES, IL-8, GM-CSF and sICAM-1 from HNEC cultures established from seasonal allergic rhinitis outside the pollen season. Results are expressed as individual (dots) and median (horizontal lines) values. (modified from Abdelaziz M.M. *et al.*, 1998).

of 0-10⁻³M fexofenadine, the main active metabolite of terfenadine, on eosinophil-induced changes in electrical resistance (measure of permeability of epithelial cultures) and release of pro-inflammatory mediators from these cells [19]. Additionally, we have studied the effect of this drug on eosinophil chemotaxis and adherence to endothelial cells, induced by conditioned medium from the NEC cultures. Incubation of the (NEC) in the presence of eosinophils treated with opsonised latex beads significantly decreased the electrical resistance of these cultures, an effect which was abrogated by treatment of the cultures with 10⁻⁹-10⁻³M fexofenadine (fig. 1). Latex beads-treated eosinophils also significantly increased the basal release of RANTES, IL-8, GM-CSF and sICAM-1, of which the release of IL-8, GM-CSF and sICAM-1 was significantly attenuated by treatment with fexofenadine (fig. 2). Analysis of the effects of conditioned medium from NEC demonstrated that this significantly increased both eosinophil chemotaxis and adherence to endothelial cells and that addition of 10⁻⁶-10⁻³M fexofenadine to the conditioned medium significantly attenuated eosinophil chemotaxis and adherence to endothelial cells. More recently, we have investigated the effect of loratadine on nitrogen dioxide (NO₂)-induced release of inflammatory mediators from primary human bronchial

epithelial cell (HBEC) cultures [20]. These studies demonstrated that exposure for 6 hours to 400 ppb NO₂ significantly increased the release of IL-8, RANTES and sICAM-1 from HBEC cultures and that the highest concentration (25 µM) of loratadine attenuated the release of all three mediators. Loratadine also attenuated the NO₂-induced release of RANTES from HBEC at a ten-fold lower concentration of 2.5 µM, and sICAM-1 at an even lower concentration of 0.25 µM.

Although the anti-inflammatory effects of antihistamines have been documented, the specific mechanisms underlying these effects are not well understood. Some studies have suggested that antihistamines can inhibit Ca-influx into cells and may therefore influence the signal transduction pathways primed by changes in cytosolic Ca²⁺ [21]. More recently, Yoneda and colleagues have demonstrated that azelastine hydrochloride can block both the activation of NF-kappa B and the expression of mRNAs for IL-β, IL-6, GM-CSF and TNFα, in human peripheral blood leucocytes and monocytes, suggesting that the anti-inflammatory activity of antihistamines may be a consequence of their ability to directly influence the activation of genes responsible for the expression and synthesis of pro-inflammatory mediators [22].

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