

Are antihistamines useful in managing asthma?

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There continues to be a great deal of interest in the anti-asthmatic role of antihistamines. Antihistamines have recently been shown to have anti-inflammatory properties that are more extensive than simply the blocking of histamine receptors. For example, new evidence suggests that the suppression of cell adhesion molecule expression occurs with these drugs. The anti-inflammatory and anti-asthmatic effects of antihistamines have been evaluated in patients with both allergic asthma and rhinitis, given the established association between allergic inflammation of the upper and lower airways, with evidence to suggest that antihistamines have clinically relevant anti-asthmatic properties. As well as conferring benefits in asthma symptom control and the measurement of lung function, studies assessing the effect of histamine receptor antagonists on bronchial hyperresponsiveness suggest that there is bronchoprotection during both methacholine and mannitol challenges. Recently, there has also been considerable interest in the effect of combining an antihistamine with a leukotriene receptor antagonist. This combination has an anti-asthmatic effect that is greater than that of either drug given alone and may be comparable to inhaled corticosteroid therapy. *Curr Opin*

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Abbreviations

AMP adenosine monophosphate
FEV₁ forced expiratory volume in 1 s
ICAM-1 intercellular adhesion molecule type 1

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Introduction

There has been renewed interest in the role of antihistamines in asthma in recent years. In the 1980s clinical and challenge studies showed the efficacy of second-generation antihistamines [1], although the doses used in such studies were often higher than the normal licensed dose, and borderline results were obtained. Table 1 details a selection of studies showing clinical asthmatic efficacy at licensed doses of antihistamines. Within the past few years, more potent antihistamines have been developed that have been shown to have anti-allergy activity extending beyond histamine receptor antagonism. Previously, antihistamines have been shown to have an effect on IL-8 production [2], the electrical resistance of nasal and bronchial mucosa after inflammatory stimuli [3,4], cell adhesion molecule expression [5,6], eosinophil survival [7] and, in the case of mizolastine, effects on arachidonic acid metabolism [8]. However, there is currently ongoing research into this area.

Although the link between asthma and rhinitis has previously been described [23], there is also continuing interest in this area of research. The asthma–rhinitis link has important implications for the use of antihistamines in airways disease, as this class of medication may play a useful role in asthma management by controlling nasal allergic disease. Perhaps for this reason, there is currently a major thrust of research exploring the use of antihistamines in managing patients with allergic rhinitis and asthma. With the recent licensing of leukotriene receptor antagonists, it has now become possible to block both histamine and cysteinyl leukotrienes. Special attention has therefore been given to the use of the combination of oral mediator blockers in the management of allergic airways disease in recent years.

This review will address evidence for the role of antihistamines in patients suffering with asthma. Attention will be focused on the anti-inflammatory properties of antihistamines, the association between asthma and rhinitis, the effects of these drugs on bronchial hyperresponsiveness, and the effect of combining an antihistamine with a leukotriene receptor antagonist. No reference will be made to the discussion in the literature over the past year as to the role of antihistamines in preventing the development of asthma [24–26], following the results of the Early Treatment of the Atopic Child (ETAC) study in 1998 [27].

Table 1. Selected studies showing anti-asthmatic efficacy of antihistamines when given at clinically relevant doses

Drug	Design	Duration	Patients	Measurement	Reference
Azelastine	r, p	12 weeks	193	Significant inhaled corticosteroid sparing effect of azelastine	[9]
Cetirizine	p, db, pl	6 weeks	93	Improvement in symptoms and reliever inhaler	[10]
Cetirizine	Prophylactic compared with terfenadine	3 weeks	43	More patients were free from symptoms with cetirizine	[11]
Cetirizine	r, p, co, db	Single dose	12	Significant increase in FEV ₁ , FEF ₂₅₋₇₅ for 8 h	[12]
Cetirizine	r, p, co, db	Single dose	10	Significant bronchodilation (FEV ₁) up to 2 h	[13]
Cetirizine	r, p, co, db	Single dose	10	Significant protection against histamine bronchial challenge	[14]
Cetirizine	r, p, co, db	2 weeks	12	Reduction in methacholine bronchial responsiveness after allergen challenge	[15••]
Cetirizine+ montelukast	r, p, co, db	2 weeks	14	Significant improvement in spirometry, symptoms and AMP bronchial challenge	[16••]
Desloratadine	r, p, pl, db	4 weeks	600	Reduction in asthma symptom and reliever inhaler	[17•]
Fexofenadine	r, p, co, db	14 h	20	Increase in mannitol PD ₁₅	[18••]
Loratadine	p, db, co	8 weeks	17	No change in symptoms, or PFT but reduction to histamine challenge	[19]
Loratadine	r, p, co, db	3 days	12	No bronchodilation or methacholine protection	[20]
Loratadine	Open	8 weeks	25	Improvement in FVC, FEV ₁ , PEF, AR, cough	[21]
Loratadine	r, co, db, addition to montelukast	2 weeks	117	Improvement in FEV ₁ , symptoms, reliever use	[22••]

co, Crossover; db, double-blind; p, placebo; pl, parallel; r, randomized. AMP, Adenosine monophosphate; AR, allergic rhinitis; FEF₂₅₋₇₅, forced mid expiratory flow; FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; PEF, peak expiratory flow; PFT, pulmonary function test.

Antihistamines as anti-inflammatory agents

For antihistamines to have an effect on asthmatic symptoms there must be evidence of a major role of histamine and mast cells in asthma. Over the past year, the role of mast cells in orchestrating the asthmatic inflammatory process has been reviewed by Hart [28•], and there is new evidence to suggest that there are increased circulating mast cell colony-forming cells in asthma [29]. In-vitro studies have demonstrated the role of histamine in activating lung macrophages and inducing exocytosis, which can be inhibited by pharmacological concentrations of fexofenadine [30•,31•].

Over recent years there has been growing evidence to suggest that antihistamines have anti-inflammatory properties that are more extensive than simply antagonizing the effect of histamine at H₁-receptors [7]. Bakker *et al.* [32•] demonstrated that more than just blocking the H₁ receptor, antihistamines such as cetirizine reduce the H₁ receptor activity by stabilizing an inactive form of the receptor. There has been considerable interest in the role of antihistamines in suppressing the expression of cell adhesion molecules, which are involved in the migration of leukocytes into tissues, as this may be a mechanism of anti-inflammation activity. Branco-Ferreira *et al.* [33•] showed that loratadine administered at a dose of 10 mg a day for one month caused a reduction in serum cell adhesion molecules in patients with seasonal allergic rhinitis. In that study the effect was shown to be additive to that of corticosteroids, as all patients were permitted to take intra-nasal budesonide during the study. This finding is in keeping with an in-vitro study in which it was shown that desloratadine significantly inhibited intercellular

adhesion molecule type 1 (ICAM-1), ICAM-1 messenger RNA and nuclear factor kappa B production from bronchial epithelial cells that were infected by rhinovirus [34•]. In another study [35•], mizolastine was shown to downregulate ICAM-1 expression on IFN- γ -stimulated nasal stromal cells, although this was only significant at 10 times the normal peak plasma concentrations of mizolastine. The authors reported a non-significant effect on nasal epithelial cells (as opposed to stromal cells), and suggested that there was a differential in response between these cell types, although there was also a trend towards suppression with epithelial cells [35•].

These and other findings have prompted reviews within the past year detailing the anti-inflammatory effects of antihistamines. In a comprehensive review, Walsh *et al.* [36••] clearly detailed in-vitro and in-vivo evidence for the anti-inflammatory activity of antihistamines, and discussed their role in asthma management. Barody and Naclerio [37••] reviewed animal work evaluating the inhibition of antihistamines on cellular infiltration into tissues, and human studies regarding the adhesion molecules of different antihistamines. Marshall *et al.* [38•] summarized the mechanisms of immune response, reviewed the different treatment strategies in allergy, and evaluated the systemic anti-inflammatory properties of antihistamines with an emphasis on desloratadine.

Anti-asthmatic activity of desloratadine

Desloratadine, the active metabolite of loratadine, was licensed for use in allergic rhinitis this year. Two review articles have appeared profiling this new drug [39•,40•], which have also specifically addressed its anti-asthmatic

efficacy in patients with seasonal allergic rhinitis and asthma. Both of these reviews referred to abstracted studies that were also discussed in more detail by Baena-Cagnani [17•] in a further article on the subject. Such studies evaluated the effect of 5 mg desloratadine in over 600 patients with seasonal allergic rhinitis and mild asthma who were treated with inhaled bronchodilators only. Significant improvements compared with placebo were found in terms of asthma symptoms, reliever inhaler requirements or spirometry over a 2–4 week duration. Unfortunately, these data are in abstract form only, and it is therefore difficult to make specific comments about the study design. However, it does show that a potent antihistamine has an effect on allergic asthma as well as rhinitis, and this is in keeping with previous data on other antihistamines [10,41,42].

Asthma and rhinitis association

It has long been recognized that there is an association between asthma and rhinitis. However, within the past year reviews have appeared detailing genetic [43•], epidemiological [44•], and immunological [45•] evidence to suggest the systemic nature of allergic disease. Indeed, it may be considered that asthma and rhinitis are different expressions of only one airways disease [46•]. Hellings *et al.* [47••] performed a novel experiment in which sensitized mice were chronically exposed on a daily basis to inhaled allergen for one week then, after 10 days free from allergen, were acutely re-exposed. Although the main site of deposition was the nasal mucosa, there was evidence of upper and lower airway eosinophilic inflammation, as determined by bronchial and nasal lavage and mucosal biopsy specimens, with associated blood eosinophilia and increased IL-5 levels, during both the chronic and acute allergen exposure. Braunstahl *et al.* [48••] performed a similar elegant study in non-asthmatic patients with allergic rhinitis, in whom bronchial and nasal biopsies were taken before and 24 h after nasal allergen challenge. The authors demonstrated an increased number of bronchial mucosal eosinophils, which correlated with increased concentrations of cell adhesion molecules and the asthmatic symptom score. Given the evidence that nasal inflammation leads to bronchial inflammation and asthmatic symptoms, antihistamines may play a useful role in the management of asthma by controlling nasal disease, with a resultant downstream effect on the lungs [49,50].

Effects of cetirizine on bronchial hyperresponsiveness

Aubier *et al.* [15••] evaluated the effect of bronchial hyperresponsiveness in 12 patients with a history of seasonal asthma and rhinitis in a placebo-controlled cross-over study. The study was conducted outside the pollen season and therefore patients had mild symptoms and normal spirometry. Patients had measurements of

spirometry (forced expiratory volume in 1 s; FEV₁; and forced vital capacity), nasal flow and bronchial hyperresponsiveness to methacholine, taken 1 h and 6 h after a nasal allergen (timothy-grass) challenge. There was no difference with cetirizine 1 h after the challenge for any of the measurements. However, although there was no difference in spirometry, there was a significant increase in nasal flow and methacholine PD₂₀ (provocative dose causing a 20% fall in FEV₁) 6 h after the challenge with cetirizine treatment.

Unfortunately, the authors wished to assess the early (1 h) and late (6 h) phase response after allergen challenge on the one occasion. Therefore patients had both challenges in quick succession. This may well have effected the second challenge, although because it was a cross-over study the circumstances were the same for both cetirizine and placebo. The authors also discounted any bronchodilatory effect of cetirizine on the results because the patients had normal spirometry before each methacholine challenge while on placebo or active treatment. The study also illustrated the asthma–rhinitis link, in keeping with previous studies [47••,48••].

Effects of fexofenadine on mannitol challenge

An interesting study by Brannan *et al.* [18••] compared the effect of an antihistamine and leukotriene receptor antagonist by using inhaled mannitol challenge. Inhaled mannitol challenge, which was developed by Anderson and colleagues [51], causes bronchoconstriction by the release of mediators from mast cells [52]. It is similar to exercise challenge testing [53], and is a predictive marker of asthmatic exacerbations [54]. Fexofenadine 180 mg and montelukast 10 mg were compared in a placebo-controlled parallel study with 20 patients with mild asthma in each arm. Measurements were made of the PD₁₅ (provocative dose causing a 15% fall in FEV₁) for mannitol and the time profile for recovery after challenge. They showed that the antihistamine caused a significantly greater PD₁₅; however, there was a longer time to recovery of FEV₁ back to baseline values. In contrast, montelukast did not significantly alter the PD₁₅; however, patients recovered significantly faster.

The paper suggests a mechanism for the additivity of these two classes of drugs. By blocking the effects of pre-formed histamine from mast cells during the acute phase of the challenge, patients were able to withstand inhaling higher concentrations of mannitol. However, after bronchoconstriction had occurred, the antihistamine had no beneficial effect, suggesting that other cytokines are involved. The longer time taken for the spirometry to return to baseline values may be a result of the increased dose of inhaled mannitol. Montelukast, on the other hand, had no effect on the initial phase of the

challenge, suggesting that histamine is the principal acute bronchoconstricting agent, but rapidly improved recovery, suggesting that this is caused by the effect of the synthesis of leukotrienes. Unfortunately, the authors did not compare the effects of the combination of drugs to determine whether the acute and recovery phases could be blocked, although the study is currently ongoing.

The additive effect of loratadine to montelukast on spirometry

Previous authors had shown the additivity of an antihistamine to a leukotriene receptor antagonist in terms of the effect of spirometry after inhaled allergen challenge [55] and seasonal allergic rhinitis symptoms [56]. However, Reicin *et al.* [22**] performed the first study to address this issue using spirometry as the endpoint. They compared 2 weeks' therapy of 10 mg montelukast plus placebo with 10 mg montelukast plus 20 mg loratadine in a multi-centre placebo-controlled, randomized crossover study in 117 patients with moderate persistent asthma. Notably, 95% had a previous history of allergic rhinitis symptoms. The addition of loratadine to montelukast demonstrated a significant improvement in the primary endpoint, which was the percentage change in FEV₁ from baseline, with 65% showing greater response with the addition of loratadine. Furthermore, there were also significant improvements in peak flow, symptoms scoring, and rescue inhaler requirement. There was no difference in the adverse effect profiles and no evidence of tachyphylaxis to response.

It was a short-term pilot study of 2 weeks' duration, although this would have been sufficient to achieve the majority of the effects of these drugs. Despite there being a statistically significant difference in the change in FEV₁ from baseline with montelukast and loratadine compared with montelukast alone, the difference only amounted to 4.15%. This is a reflection of the relative insensitivity of spirometry as a measure of treatment response in patients with this severity of asthma, and the reason that a relatively large number of patients were required in this crossover study. Interestingly, the authors also showed that the combination with loratadine resulted in a significantly higher increase in FEV₁ after β -agonist therapy, which suggests that the beneficial effect of antihistamines is in addition to this class of therapy.

Antihistamines in combination with leukotriene receptor antagonists

Combination therapies in asthma have been discussed previously in this journal [57*], with attention given to the use of combined antihistamines and leukotriene receptor antagonists. In an editorial published earlier this

year, Sampson and Rorke [58**] reviewed the beneficial effects of combining an antihistamine and leukotriene receptor antagonist together to treat allergic disease. They also discussed evidence for the involvement of both histamine and cysteinyl leukotrienes in asthma, and allergic skin and nasal disease. Recently, a study was published [59] which showed no difference between the combination of cetirizine plus montelukast and intranasal mometasone when treating patients with seasonal allergic rhinitis, with both treatments being superior to placebo.

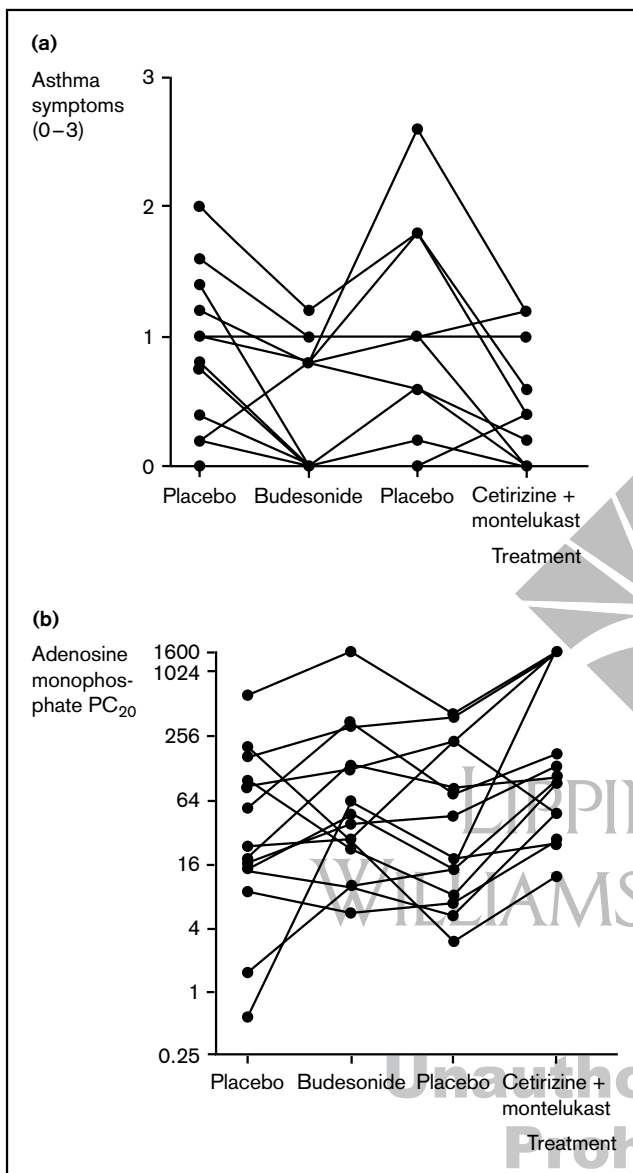
Ruck *et al.* [60**] performed an in-vitro study that suggested that there is a synergistic rather than an additive effect of the combination of selective histamine and leukotriene receptor antagonists. The study investigated the effect of these drugs, given alone or in combination, on the inhibition of anti-human IgE antibody-induced contraction of isolated human bronchial smooth muscle. At the concentrations used, neither chlorpheniramine (15%) nor MK-571 (36%) produced significant inhibition of the contraction, but the combination produced nearly complete inhibition (87%). The findings may be caused by the concentrations used, and perhaps a more potent antihistamine would have had greater effects when given alone. However, it does explain the findings of Reicin *et al.* [22**].

Comparison of cetirizine and montelukast versus budesonide

Given the additive/synergistic effects of antihistamines and leukotriene receptor antagonists, we decided to compare this combination with inhaled plus intranasal corticosteroids [16**], the current gold standard anti-inflammatory therapy. The anti-asthmatic efficacy of 400 μ g inhaled budesonide plus 200 μ g intranasal budesonide versus 10 mg oral montelukast plus 10 mg oral cetirizine in patients with seasonal allergic rhinitis and asthma was evaluated in a placebo-controlled crossover study. There were significant improvements in domiciliary peak expiratory flow rate, rescue inhaler requirements, asthma symptoms (Fig. 1a), and the daily activity score with both treatments, but there was no difference between the two treatment groups. Using adenosine monophosphate (AMP) bronchial challenge testing (Fig. 1b), an improvement compared with placebo was seen for montelukast plus cetirizine, but not for budesonide. Although for exhaled nitric oxide there was significant suppression with the corticosteroid but not the combined mediator antagonists.

It was a short-term (2 weeks) pilot study that only recruited 14 patients. Furthermore, the laboratory data need to be treated with caution. Exhaled nitric oxide has been shown to be particularly sensitive to the effects of inhaled corticosteroids, with low doses up to 400 μ g per

Figure 1. Combined mediator blockade versus topical corticosteroids in asthma and rhinitis



Individual scatter plots for patients' response with both placebo periods, inhaled and intra-nasal budesonide and with oral cetirizine and montelukast for (a) asthma symptom score and (b) adenosine monophosphate bronchial challenge. The solid line links the response for each patient.

day resulting in the near normalization of levels despite continuing bronchial hyperresponsiveness [61]. AMP causes bronchoconstriction by the release of mast cell mediators, and therefore specifically blocking their activity may result in protection of the bronchoconstrictive effects of this stimulus. However, in terms of the patients' symptoms, rescue inhaler requirements, and peak expiratory flow rate there were significant improvements with both topical treatments when compared with placebo.

Conclusion

There is increasing evidence that antihistamines have clinically beneficial effects on asthma disease control. This is perhaps caused by the anti-inflammatory nature of these drugs, or the beneficial effect of treating upper airway disease on the control of lower airway inflammation. At present there is little evidence that antihistamines should be used as first-line therapy for asthma. However, they play a useful role in managing asthma in patients with concomitant allergic rhinitis, or when used in combination with leukotriene receptor antagonists.

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