

An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma

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Summary

Background Nasal polyposis occurs frequently in patients with intrinsic asthma, especially in those who are aspirin sensitive. It can be difficult to treat effectively, even with surgery and regular topical intranasal corticosteroids many patients are still symptomatic.

Objective To investigate the response to montelukast, a leukotriene D₄ receptor antagonist, as an add-on therapy to topical and inhaled corticosteroids in patients, both aspirin sensitive (AS) and aspirin tolerant (AT), with nasal polyposis and asthma.

Methods Nasal polyposis symptoms were assessed by visual analogue scales; nasal polyps were assessed by nasendoscopy and via the measurement of nasal volumes by acoustic rhinometry. The nasal airway was assessed by nasal inspiratory peakflow (NIPF). Asthma was monitored using symptom scores and peak expiratory flow measurements. Aspirin sensitivity was assessed by history together with intranasal lysine aspirin challenge. Upper and lower airway nitric oxide measurements were made before and during treatment.

Results Clinical subjective improvement in nasal polyposis occurred in 64% AT ($P < 0.01$), patients and 50% AS patients ($P > 0.05$); asthma improvement in 87% AT and 61% AS patients ($P < 0.05$ for both). Objective changes in peak flow occurred only in AT patients ($P < 0.05$). Acoustic rhinometry, nasal inspiratory peak flow and nitric oxide levels did not change significantly in any group, however, correlations were seen between nitric oxide levels and polyp scores and between nitric oxide levels and acoustic rhinometry changes. Improvement on montelukast therapy was not associated with any of the following variables: age, sex, skin prick test positivity, disease duration or aspirin sensitivity. ($P > 0.05$ for all).

Conclusion The findings are consistent with a subgroup of nasal polyps/asthma patients in whom leukotriene receptor antagonists are effective. This is not related to aspirin sensitivity. Further placebo-controlled studies need to be undertaken.

Keywords: nasal polyposis, montelukast, asthma, leukotrienes, aspirin sensitivity, leukotriene receptor antagonists

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Introduction

Nasal polyposis is a relatively common disease affecting 0.2% to 1% of the adult population in the United Kingdom at some time in their lives [1]. It is more common when nasendoscopy is undertaken in asymptomatic patients. In

asthmatics the frequency of polyps increases to 15% with age > 50 , being more frequent in non-atopic patients reaching a peak frequency of 30% in patients with acetylsalicylic acid intolerance of the bronchospastic type [2–6].

The objectives of management of nasal polyposis are to eradicate nasal polyps, eliminate symptoms and prevent recurrence. In fact, most clinicians treat patients on an

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individual basis modulating long-term intranasal corticosteroids, short-term systemic steroids and surgical treatment as appropriate [7,8]. However, the recurrence rate is generally high and is aggravated in patients with positive allergy skin tests and those with aspirin intolerance [9,10]. Even topical steroids, the mainstay of treatment, have been shown to delay, but not to prevent recurrence [11–16]. As the goal of management cannot be reached in all patients, further studies are warranted in order to improve management of this disease.

Leukotrienes, derivatives of arachidonic acid, are generated during allergic and inflammatory respiratory diseases [17–19]. Leukotriene D₄ was recovered from nasal lavage secretions after allergen provocation and is known to contract smooth muscle, increase blood vessel permeability, induce glandular hyper-secretion and increase nasal blood flow and airway resistance [20–23]. Okuda reported that the duration of leukotriene D₄-induced increase in nasal resistance exceeded that of histamine and was similar to that observed after allergen challenge [24]. Asthmatic airways were also found to respond by bronchoconstriction to inhaled leukotrienes [25,26]. These properties have enabled the pharmacological evaluation of a number of leukotriene receptor antagonists [27–32]. One such compound is MK-0476 (montelukast) which has recently shown to be a highly potent and long-standing antagonist of leukotriene D₄-induced bronchoconstriction in patients with asthma [33–38]. However, in contrast to asthma its predicted role in management of nasal polyps is not yet evaluated. In this study our aim is to evaluate the efficacy and tolerability of montelukast as an add-on therapy in the treatment of nasal polyposis in association with asthma.

The fact that in aspirin sensitive (AS) individuals leukotriene production is increased and yet there is exquisite sensitivity to leukotrienes, means that it is amongst this group of patients that antileukotrienes are likely to prove most effective.

Materials and methods

The study involved 44 adult patients (19 males), mean age 51 ± 2.2 years, range 21–78 years with nasal polyposis refractory to medical therapy with long-term intranasal corticosteroids. Twenty-four of these were previously diagnosed as having aspirin sensitivity (AS) on the basis of their history and confirmation with lysine aspirin nasal challenge (vide infra). Challenges were also undertaken in patients who did not have a history of recent tolerance to oral aspirin or non-steroidal anti-inflammatory drugs (NSAIDs).

Patients with any significant concurrent illness, upper or lower respiratory tract infection within one week and/or use of systemic corticosteroids within two weeks prior to the inclusion visit were excluded from the study.

The following criteria were assessed in all patients: history including aspirin sensitivity and asthma, nasal symptoms (obstruction, anosmia, sneezing, rhinorrhoea and itching), chest symptoms (including cough, wheezing, shortness of breath, sputum production and nocturnal waking), nasendoscopy, peak expiratory flow rate and skin prick testing to 10 common inhalant allergens. Twenty-eight patients were able to record repeatable values on the nasal inspiratory peak flow meter, a subset of 16 underwent acoustic rhinometry both pre- and post-montelukast therapy. These patients also had levels of nitric oxide recorded in nose and chest.

Our regimen included a three-month trial of montelukast, 10 mg daily, as an add-on therapy to intranasal and inhaled corticosteroids. Patients were assessed at the end of this time and were given a clinical score (+2 for significant improvement, +1 for mild to moderate improvement, 0 for no significant change, –1 for slight deterioration and –2 for significant deterioration). These scores were based on patient symptoms, examination findings and their peak flow charts. Acoustic rhinometry and peak expiratory flow rates were also reassessed. Three patients were unable to tolerate montelukast due to adverse events (nausea, insomnia, indigestion) and were not included in the final analysis.

Acoustic rhinometry

This was performed as previously described [39]. Repeated measurements were performed and the mean of five values was recorded, provided the coefficient of variation was less than 5%.

Peak expiratory flow rate

This was performed in triplicate with the best of three values being recorded and expressed as the percentage of the mean predicted value.

Lysine aspirin intranasal challenge

This was used to test for aspirin sensitivity. Baseline measurements of nasal symptoms, acoustic rhinometry, nasal inspiratory peak flow and pulmonary peak flow were made. Placebo challenge was given with 100 µL normal saline, prewarmed to body temperature, into each nasal cavity. The measurements were repeated at 15 min. Provided no significant changes (vide infra) had occurred then further challenge was given with 8 mg of lysine aspirin, 4 mg to each nostril in 100 µL of normal saline. This was freshly prepared using capsules (Laboratories for Applied Biology, London, UK), of lysine aspirin dissolved in saline. Repeat measurements were made at 20, 40 and

60 min post-challenge. Most aspirin sensitive patients began to react at about 45 min

A positive response was said to have occurred if symptoms increased by over 50% or there was a decrease on acoustic rhinometry Amin or nasal volume of more than 25%. If the response was equivocal with values around 25% then nasal inspiratory peak flow was taken into consideration and a decrease of over 50% regarded as positive. Our previous results show this test to have a specificity of 87% and a sensitivity of 70%. Pulmonary peak flow was also recorded, but rarely dropped more than 15%.

If no response occurred the challenge was repeated using 16 mg lysine aspirin.

Nitric oxide analysis

This was performed by chemiluminescence using the Logan-Sinclair analyser (Logan Research Ltd, Rochester, Kent, UK). Recordings were made from both sides of the nose and from the lower respiratory tract [40].

Statistical methods

Applicable data were expressed as mean $\pm$ SEM. Students *t*-test, where applicable, or ANOVA followed by Tukey's posthoc test were used to test the statistical significance. Pearson's correlation was used to test the statistical significance of any possible correlation. *P*-values < 0.05 were considered significant.

Results

Aspirin sensitivity

Out of the 41 patients included in the final analysis 24 were aspirin sensitive (AS), 17 were aspirin tolerant (AT). Eighteen of the 24 AS patients (75%) were skin prick test positive to one or more common allergens, nine of the 17 AT patients (53%) were positive.

Clinical scores

(Figure 1) There was a tendency for more of the AT patients to show improvement (64% for polyp score, 87% for asthma score), when compared to the AS patients (50% for polyp score, 61% for asthma score). This difference did not reach statistical significance. Aspirin sensitive patients tended to be worse at the start of treatment having lower peak flows, higher pulmonary nitric oxide levels and lower nasal nitric oxide levels (indicative of nasal obstruction), with lower nasal volumes on acoustic rhinometry, but these did not reach statistical significance.

Change in clinical polyp score was significant for all

patients ($P < 0.01$); this was true for the AT ($P < 0.01$), but not the AS subgroup ($P > 0.05$).

The change in asthma scores were significant for all patients and within both subgroups ($P < 0.05$). The change in asthma score correlated significantly with the change in polyp score at the 95% confidence level. A cross tabulation of these results is shown in Table 1.

There were more patients showing marked improvement in the AS group both with respect to polyps and asthma, compared to the AT group which had more mild to moderate improvement.

Objective measurements

Peak expiratory flow rate (Figs 2a and b). When peak flow measurements were compared before and after montelukast there was a significant improvement within the AT subset ($P < 0.05$), but not within the group as a whole nor in the AS patients. Comparison of AS and AT groups did not show a significant difference.

Nasal inspiratory peak flow Values did not change significantly in any group, nor did the volume measurement on acoustic rhinometry. However, there was a trend in that the mean change in those patients with improved polyp scores was -0.4 ($n = 10$) whereas it was -10.5 in those with clinical deterioration in their polyps ($n = 6$), $P = 0.06$.

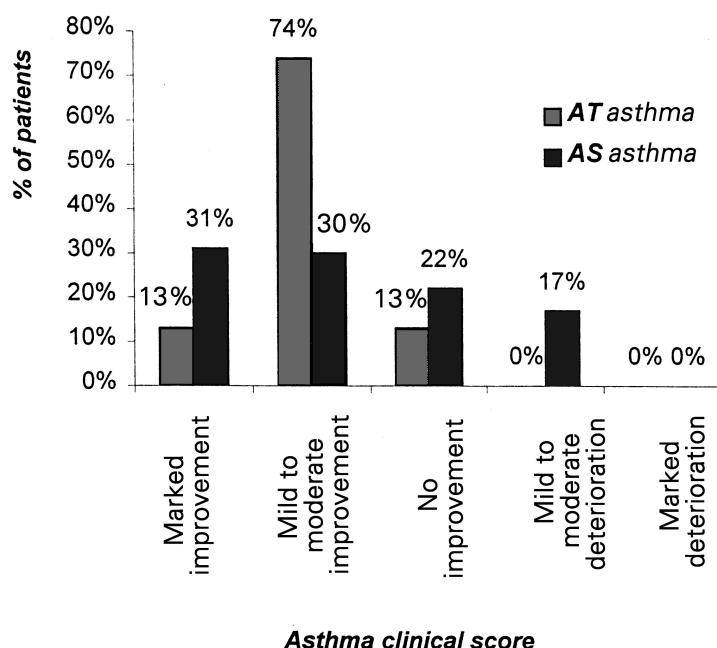
Nitric oxide Nitric oxide levels were low (< 500 ppb) in the noses of polyp patients. They tended to rise on treatment with montelukast, but changes were not significant, however, nasal nitric oxide changes correlated significantly with polyp score changes as well as the acoustic rhinometry volume changes ($P < 0.05$ for both), but not with nasal inspiratory peak flow changes. Pulmonary nitric oxide changes were not significant in any group.

Improvement on antileukotriene therapy was not associated with any of the following variables: age, sex, skin prick test positivity, disease duration or aspirin sensitivity ($P > 0.05$).

Discussion

A placebo-controlled, double-blind trial would obviously have been preferable to an open audit in these patients. Unfortunately we were unable to obtain montelukast and placebo for this purpose. The placebo effect of new medication is undoubted and therefore we continued the study for three months in order to allow any initial patient enthusiasm to dissipate. Nevertheless the figure of 50% improvement may need revising when placebo-controlled studies are available. The correlation between asthma

(a)



(b)

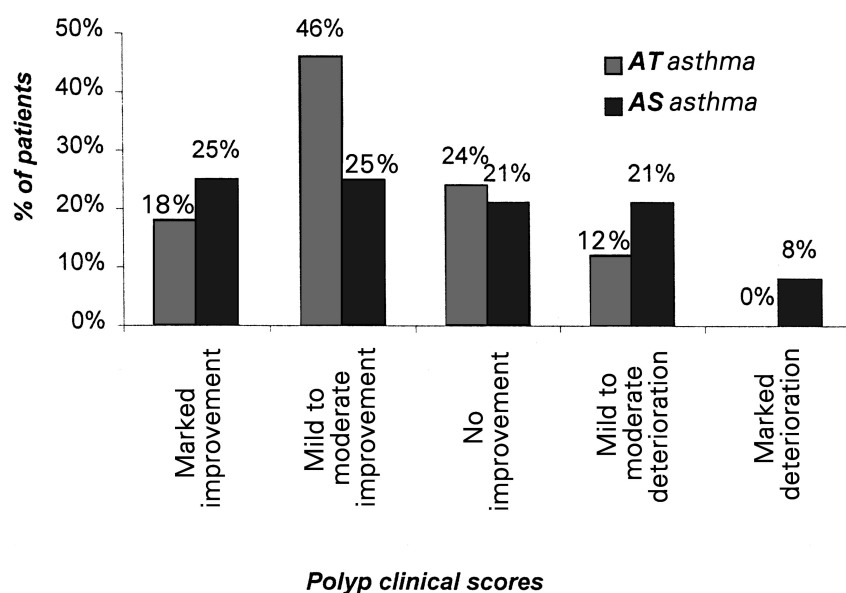


Fig. 1. (a). Clinical scores of aspirin tolerant (AT) and aspirin sensitive (AS) patients. $P < 0.05$ in AT asthma comparing scores pre- and post-montelukast $P < 0.05$ in AS asthma comparing scores pre- and post-montelukast. (b). Clinical scores of polyp tolerant and polyp sensitive patients. $P < 0.01$ in AT polyps comparing scores pre- and post-montelukast. $P > 0.05$ in AS polyps comparing scores pre- and post-montelukast.

scores and peak flow change does suggest that the clinical impression has a real basis. The proportion of improvement corresponds with that found by Uluap *et al.* in whose study 9/15 patients with aspirin triad disease showed some improvement [41].

The clinical response to montelukast appeared to be more impressive with respect to asthma than to nasal polyposis, possibly suggesting that leukotrienes are more relevant in the lower than in the upper airway. Previous studies also showed that leukotriene receptor antagonists

Table 1 Cross tabulation of polyp and asthma clinical scores

Polyps clinical score	Asthma clinical score as percentage within polyp clinical score				
	Marked improvement	Mild to moderate improvement	No change	mild to moderate deterioration	marked deterioration
Marked improvement	75%	12.50%	12.50%	0%	0%
Mild to moderate improvement	23.10%	69.20%	7.70%	0%	0%
No change	0%	62.50%	25%	12.50%	0%
Mild to moderate deterioration	0%	42.80%	28.60%	28.60%	0%
Marked deterioration	0%	0%	50%	50%	0%

were effective in the treatment of asthma [42–46]. In our study more AT patients tended to experience benefits than AS patients with respect to both conditions, though this experience did not reach statistical significance. This was surprising in view of the probable role of leukotrienes in aspirin sensitivity. However, the AS patients contained a higher proportion of marked responders suggesting that in this group the antileukotrienes either had little or no effect, or worked well, i.e. that only a proportion of patients are responders.

The clinical response was more dramatic than objective measurements such as peak flow, nasal inspiratory peak flow, and acoustic rhinometry would indicate, although the correlations between peak flow changes and asthma score change and between polyp scores, nasal nitric oxide and acoustic rhinology volume changes, all suggest that the clinical improvement has a genuine basis. Some of the

patients felt better on the drug without significant changes in any objective parameter. Recent studies in allergic rhinitis using the combination of montelukast and loratadine has shown that this is significantly better than either drug used alone [47]. However, this combination is not as effective as a nasal steroid [48]

As we have previously noted, nitric oxide levels tend to be low in nasal polyposis and decrease with increasing polyp volume [49]. Thus the increased levels seen with montelukast therapy probably reflect some opening of the ostiomeatal complex since nitric oxide arises predominantly in the paranasal sinuses. Conversely, in those who did not improve, nitric oxide levels tended to fall. The correlation between nasal nitric oxide changes, polyp scores and acoustic rhinometry volume measurements suggest that the major symptomatic effect of polyps is at the ostiomeatal complex level. The lack of correlation with

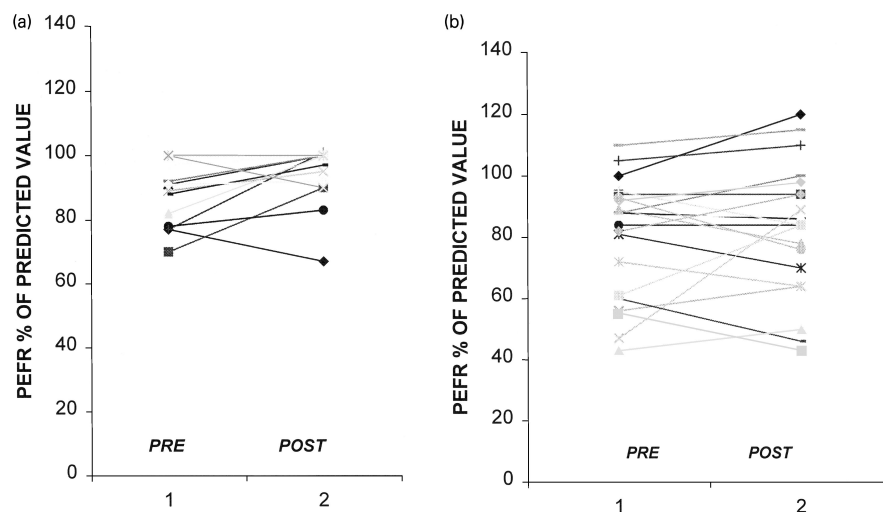


Fig. 2. (a). Peak expiratory flow rates (PEFR) (% of predicted value) of aspirin tolerant (AT) patients. $P < 0.05$ in AT PEFR comparing pre- and post-montelukast. (b). Peak expiratory flow rates (% of predicted value) of aspirin sensitive (AS) patients. $P > 0.05$ in AS PEFR comparing pre- and post-montelukast.

nasal inspiratory peak flow is not unexpected since in many polyp patients the lower nasal airway is preserved.

Unfortunately we were unable to find any predictive parameter for responsiveness to montelukast. The variation in response suggests that cysteinyl-LT may play a greater role in disease in some individuals than in others in whom different mediators such as histamine or prostaglandins may be of greater importance. Leukotrienes may also be of more importance in the lung than in the upper airway. It is difficult to reconcile this explanation with the theory that aspirin sensitive disease occurs because of cyclo-oxygenase inhibition of prostaglandin synthesis leading to increased leukotriene production. Our aspirin sensitive patients were unusual in that they were predominantly atopic (75%), whereas previous authors have reported aspirin sensitivity as having a prevalence of atopy close to that of the normal population (20%). It is conceivable that aspirin sensitivity is itself heterogeneous and that in some patients there is a sensitization to aspirin: positive skin pricks to aspirin do occur and only a proportion of AS patients exhibit sensitivity to salicylate-containing foods, a phenomenon which is difficult to explain on a Cox 1 inhibition basis.

Another possible explanation for the heterogeneity of response is polymorphism of the leukotriene receptor. Recently a second leukotriene receptor has been described, at which montelukast, zafirlukast and pranlukast exhibited low potency in competition for LTD₄ binding [50]. This receptor may be more frequent among aspirin sensitive individuals, in which case an inhibitor of leukotriene synthesis might prove more effective in this group. Clinical experience with zileuton has shown some return of olfaction in nasal polyposis [51].

Nasal polyposis associated with asthma is a difficult condition both for the patients and their doctors. The addition of an antileukotriene drug may prove helpful in approximately half of these patients and is worth a trial therapy.

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