

A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma

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Summary

Background Allergic rhinitis and asthma commonly coexist and are both mediated by similar inflammatory mechanisms. Leukotriene antagonists may therefore be an alternative to corticosteroid therapy.

Objective To compare oral montelukast with inhaled plus intranasal budesonide in patients with seasonal allergic rhinitis and asthma.

Patients and methods A single-blind double-dummy placebo-controlled crossover study was performed comparing once daily 10 mg oral montelukast with 400 µg inhaled plus 200 µg intranasal budesonide in 12 patients with allergic rhinitis and asthma: mean (S.E.) age 34.0 years (2.7), forced expiratory volume in 1 s (FEV₁) 91.2 (3.8)% predicted. Each treatment was for 2 weeks with a 1-week placebo run-in and washout. Measurements were made after each active treatment and placebo for: adenosine monophosphate bronchial challenge, exhaled and nasal nitric oxide. Patients also recorded their domiciliary peak expiratory flow, nasal peak inspiratory flow, asthma and seasonal allergic rhinitis symptoms.

Results There were no significant differences between the placebos for any measurement. For adenosine monophosphate PC₂₀, geometric mean fold differences (95% confidence interval (CI) for difference) were 6.4 (2.2–18.6) for placebo vs. budesonide, 2.9 (1.0–8.4) for placebo vs. montelukast, and 2.1 (1.1–4.5) for budesonide vs. montelukast. For exhaled nitric oxide (p.p.b.) there was significant ($P < 0.05$) suppression with both montelukast (10.9) and budesonide (10.1) compared with placebo (18.8). For nasal nitric oxide and nasal peak flow there were only significant differences with budesonide compared with placebo. Both treatments reduced total seasonal allergic rhinitis symptoms but only budesonide had a significant effect on nasal symptoms.

Conclusion Once-daily inhaled plus intranasal budesonide and once daily montelukast showed comparable efficacy on lower airway, but only the budesonide had significant efficacy on upper airway inflammatory markers. Both treatments significantly reduced allergic rhinitis symptoms.

Keywords: asthma, allergic rhinitis, corticosteroid, leukotriene antagonist, adenosine monophosphate, bronchial hyperreactivity

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Introduction

Asthma and allergic rhinitis are two common conditions, both occurring with increasing prevalence, which frequently coexist. Indeed approximately 60% of patients with

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Table 1 Mean (S.E.M.) values for 1st (run-in) and 2nd (washout) placebo in sequence for adenosine monophosphate bronchial challenge PC₂₀ (AMP), exhaled nitric oxide (NO), forced expiratory volume in 1 s (FEV₁), morning peak expiratory flow rate (PEFR), evening peak expiratory flow rate, asthma symptoms, rescue inhaler usage, nasal nitric oxide, morning nasal peak inspiratory flow rate (PIFR), evening peak inspiratory flow rate, total seasonal allergic rhinitis symptoms (SARS), nasal symptoms, eye symptoms, throat symptoms, ocular sodium cromoglycate use (ocular cromoglycate), and effect of symptoms on patients' daily activity (daily activity)

	First PL	Second PL		First PL	Second PL
AMP (mg/mL)	23.5 (6.4)	34.5 (8.4)	Nasal NO (p.p.b.)	949.8 (97.5)	797.5 (87.8)
Exhaled NO (p.p.b.)	17.4 (2.0)	13.6 (1.8)	Morning PIFR (L/min)	98.8 (5.3)	110.4 (4.7)
FEV ₁ (% predicted)	89.3 (2.6)	90.3 (2.2)	Evening PIFR (L/min)	114.4 (6.6)	122.1 (5.8)
Morning PEFR (L/min)	399.2 (7.7)	398.4 (6.4)	SARS (units)	6.7 (0.9)	4.3 (0.7)
Evening PEFR (L/min)	393.6 (20.4)	425.4 (17.8)	Nasal symptoms (units)	4.5 (0.6)	2.9 (0.5)
Asthma symptoms (units)	1.2 (0.2)	0.8 (0.2)	Eye symptoms (units)	2.4 (0.4)	1.4 (0.4)
Rescue inhaler (puffs/day)	2.0 (0.5)	1.9 (0.4)	Throat symptoms (units)	0.6 (0.2)	0.7 (0.1)
Daily activity (units)	2.3 (0.5)	3.0 (0.4)	Ocular cromoglycate (units)	0.7 (0.2)	0.3 (0.1)

Values for AMP PC₂₀ are given as geometric mean.

seasonal allergic rhinitis have concomitant asthma [1]. This is mainly due to the common aetiology of both diseases; however, other explanations include an increased incidence of mouth breathing with rhinitis due to nasal obstruction [2], post-nasal drip of secretions from the nose into the trachea, and the effect of nasal inflammation on asthma [3].

Topically delivered inhaled and intranasal corticosteroids are widely recognized to be effective anti-inflammatory treatments for both conditions [4,5]. Leukotriene receptor antagonists, however, have been shown to have anti-inflammatory properties and to have beneficial effects on asthma disease control [6] and more recently in the management of allergic rhinitis. As orally administered leukotriene antagonists act systemically, in theory both conditions may be treated simultaneously.

We wished to evaluate whether an oral leukotriene receptor antagonist would be effective in patients with

seasonal allergic rhinitis and asthma, and also how it would compare with inhaled and intranasal corticosteroids. In keeping with most treatment regimes for allergic rhinitis, and to maximize compliance, we administered our treatment once daily. We therefore used inhaled plus intranasal budesonide and oral montelukast as these are the only treatments in their class which are currently licensed for once daily administration.

The primary aim was to evaluate surrogate markers of upper and lower airway inflammation. Adenosine monophosphate challenge was used as it acts as an indirect bronchoconstrictor stimulus via release of inflammatory mediators from primed mast cells—hence may be considered to be a surrogate marker of allergic airway inflammation [7]. Exhaled and nasal nitric oxide can also be used to assess the degree of airway inflammation [8]. We also measured domiciliary inspiratory nasal flow which

Table 2 Mean (S.E.M.) values after run-in placebo (PL) and after active treatment with budesonide (BUD) or montelukast (MON)

Treatment	PL	BUD	MON	Treatment	PL	BUD	MON
FEV ₁ (% predicted)	89.3 (2.6)	94.3 (2.1)	91.3 (2.1)	Evening PIFR (l/min)	114.4 (6.6)	135.7 (5.6)	124.0 (5.5)
Morning PEFR (L/min)	399.2 (7.7)	424.3 (6.2)	401.1 (6.1)	SARS (units)	6.7 (0.9)	1.8* (0.7)	3.5* (0.7)
Evening PEFR (L/min)	393.6 (20.4)	441.7 (17.3)	432.5 (16.8)	Nasal symptoms (units)	4.5 (0.6)	1.3* (0.5)	2.8 (0.5)
Asthma symptoms (units)	1.2 (0.2)	0.5 (0.2)	0.9 (0.2)	Eye symptoms (units)	2.4 (0.4)	0.4* (0.3)	0.9* (0.3)
Rescue inhaler (puffs/day)	2.0 (0.5)	0.7 (0.4)	1.5 (0.4)	Throat symptoms (units)	0.6 (0.2)	0.4 (0.1)	0.6 (0.1)
Daily activity (units)	2.3 (0.5)	1.2* (0.4)	1.5 (0.4)	Ocular cromoglycate (units)	0.7 (0.2)	0.2 (0.1)	0.3 (0.1)

Abbreviations as Table 1.*Significant ($P < 0.05$) difference between active treatments and placebo.

exhibits comparable results to rhinomanometry [9]; and patients recorded their asthma symptoms and seasonal allergic rhinitis symptoms in terms of eye, throat and nasal symptoms, in keeping with international guidelines [10].

Patients and methods

Patients

Twelve patients with seasonal allergic rhinitis and asthma (three males), mean (S.E.) age 34.0 (2.7) years, forced expiratory volume in 1 s (FEV₁) 91.2 (3.8)% predicted were recruited into the study. All patients had stable mild persistent asthma and symptomatic seasonal allergic rhinitis according to defined criteria [10,11]. Six patients were taking inhaled corticosteroids (budesonide 400 µg/day, *n* = 2; beclomethasone 500 µg/day *n* = 2, 400 µg/day *n* = 1, 200 µg/day *n* = 1), three were taking intranasal corticosteroids (beclomethasone 400 µg/day) and five were taking oral antihistamines (loratadine 10 mg/day *n* = 3, cetirizine 10 mg/day *n* = 2). All patients were required to be responsive to adenosine monophosphate challenge testing with a provocation concentration producing 20% fall in FEV₁ of <200 mg/mL (geometric mean 29 mg/mL). All patients had a positive skin prick test to grass or tree pollens and nine patients also had positive skin prick test to house dust mite. No subject had received oral corticosteroids or antibiotics for 6 months prior to the study. All subjects were non-smokers and had normal full blood count, biochemical profile and urinalysis. Approval for the study was obtained from the Tayside Medical Ethics Committee and all patients gave their written informed consent.

Methods

The study was of a randomized placebo-controlled, single-blind, double-dummy, cross-over design. Patients were enrolled during June and July 1998 when grass and tree pollen levels are highest in the Dundee area. Patients were randomized to receive the following for 2 weeks, all given once daily at 08.00 h: (i) 400 µg inhaled budesonide dry powder (as Pulmicort Turbuhaler; Astra Zeneca, Kings Langley, Herts, UK, as two puffs of 200 µg per actuation) plus 200 µg intranasal aqueous budesonide (as Rhinocort AquaTM; Astra Zeneca, as one squirt of 100 µg in each nostril) plus placebo tablets; or (ii) 10 mg oral montelukast (as SingulairTM; Merck Sharp & Dohme Ltd, Hoddesdon, Herts, UK) plus placebo nasal spray and placebo Turbuhaler. Prior to each treatment (i.e. run-in period), and at cross-over (i.e. washout period), patients had a 1-week period with placebo Turbuhaler (two inhalations), placebo nasal spray (one squirt in each nostril) and placebo tablets

all taken at 08.00 h. Six patients started with oral montelukast and six patients started with budesonide.

Laboratory-based measurements (i.e. bronchial challenge, spirometry, nitric oxide) were all made after the 1-week run-in and washout placebo periods and at the end of each of the 2-week treatment periods. Measurements were made at trough at 24 h after the last dose of active treatment or placebo.

The Turbuhalers and nasal sprays were masked and sealed in envelopes by a pharmacist along with instruction sheets at the beginning of the trial. Prior to the study and at each visit, subjects were given detailed tuition, by a third party, in how to use their nasal sprays and Turbuhaler. Nasal sprays were primed according to manufacturer's instructions and patients had to demonstrate adequate technique using Turbuhaler usage trainer (Astra Draco, Lund, Sweden) before progressing through the study. All subjects received a written instruction sheet, based on the manufacturer's recommended advice, to follow while taking their medication at home, and a simple tick chart was used as an aid to compliance. Data from patients with >90% compliance was considered to be evaluable.

Measurements

Adenosine monophosphate challenge testing Adenosine monophosphate bronchial challenge testing was performed as previously described [12] between 08.00 h and 10.00 h, after patients had withheld their reliever medication for 12 h. In brief, adenosine monophosphate, which had been prepared fresh daily, was administered in doubling cumulative doses given at 5-min intervals until fall in FEV₁ ≥ 20% was recorded. The PC₂₀ was calculated using a computer-assisted curve fitting package (Biolab Assistant 1.1; University of Dundee, UK) and interpolation of the steep part of the log dose–response curve. A value of 1600 mg/mL was assigned if the FEV₁ did not fall below 20% of baseline value.

Exhaled and nasal nitric oxide Patients had a measurement of exhaled and nasal nitric oxide (NO) using an integrated, LR2000 clinical, real-time, nitric oxide gas analyser with an accuracy of 2 p.p.b. NO and a response time of 2 s (Logan Research, Rochester, UK) using the procedures described by Kharitonov *et al* [13]. For exhaled NO, the conditions of temperature (20°C), flow rate (250 mL/min) and mouth pressure (70 mmH₂O) were standardized throughout the study [14]. Nasal NO was measured during breath-holding as assessed by simultaneous measurement of exhaled CO₂. Three measures of NO were taken and the results were analysed as the mean of the three values. The analyser was calibrated weekly using a cylinder

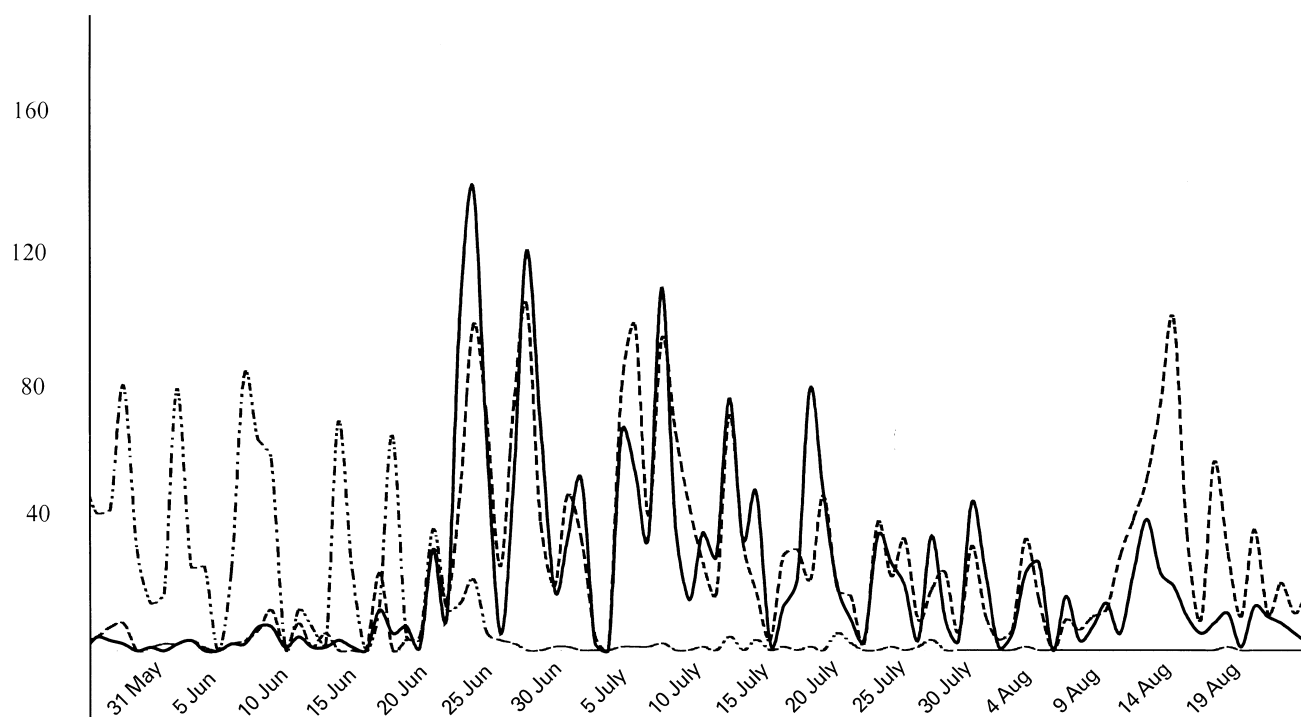


Fig. 1 Pollen counts for mixed tree, grass and weed pollens (per m^3) for the local area of the study from 21 April 1998 to 24 August 1998. $\cdots$, Tree pollen; —, grass pollen; - - -, weed pollen.

of NO at concentration of 108 p.p.b. according to manufacturer's instructions.

Spirometry Spirometry was performed according to American Thoracic Society criteria [15] using a Vitalograph compact spirometer (Vitalograph Ltd, Maids Moreton, Buckinghamshire, UK) with a pneumotachograph head and pressure transducer which was calibrated daily using a precision syringe (Vitalograph Ltd).

Diary card data Patients filled in a daily diary card in the morning and evening during the placebo and active treatment limbs. Patients measured their peak expiratory flow using a Mini-Wright peak flow meter (Clement Clarke, Harlow, UK). Nasal inspiratory flow rate was measured using an In-checkTM flow meter (Clement Clarke) while in the sitting position with a good seal around a purpose-built facemask after blowing of the nose. Patients inspired forcefully from residual volume to total lung capacity with their mouth closed. For both peak expiratory flow and nasal peak inspiratory flow measurements were made at the same time each day at 08.00 h and 22.00 h and patients recorded the highest of three readings. Patients recorded their seasonal allergic rhinitis symptoms, under 'runny nose', 'blocked/stuffy nose', 'itchy nose', 'sneezing', 'itchy eyes', 'watery eyes', 'red eyes' and 'tickly throat', as well as asthma symptoms in the morning and

evening. All symptoms were documented according to a 4-point scale with 0 indicating no symptoms and 3 indicating severe symptoms. Patients were also asked to record how much their symptoms were interfering with their daily activity on an 11-point scale, with 0 representing no symptoms and 10 representing maximal symptoms.

Skin prick testing Patients withheld antihistamine medication for 4 days prior to skin prick testing. This was performed following a standard protocol (Bencard testing solutions, Welwyn Garden City, UK) using extracts including grass, tree and weed pollens in addition to a negative control. Results were read after 10 min, a positive reaction being defined as a minimum weal diameter of 3–5 mm with erythema, at least 2 mm greater than diluent.

Pollen count measurement Data were collected locally (Scottish Crop Research Institute, Dundee, UK) using a 7-day recording volumetric spore trap (Burkard Manufacturing Co Ltd, Rickmansworth, Hertfordshire, UK) (Fig. 1).

Statistical analysis

The study was powered at the 80% level to detect a 1.0 doubling dose difference (2.0-fold) in adenosine monophosphate at 10 (the primary endpoint) with the α error set at 0.05 (two-tailed). The data for adenosine monophosphate

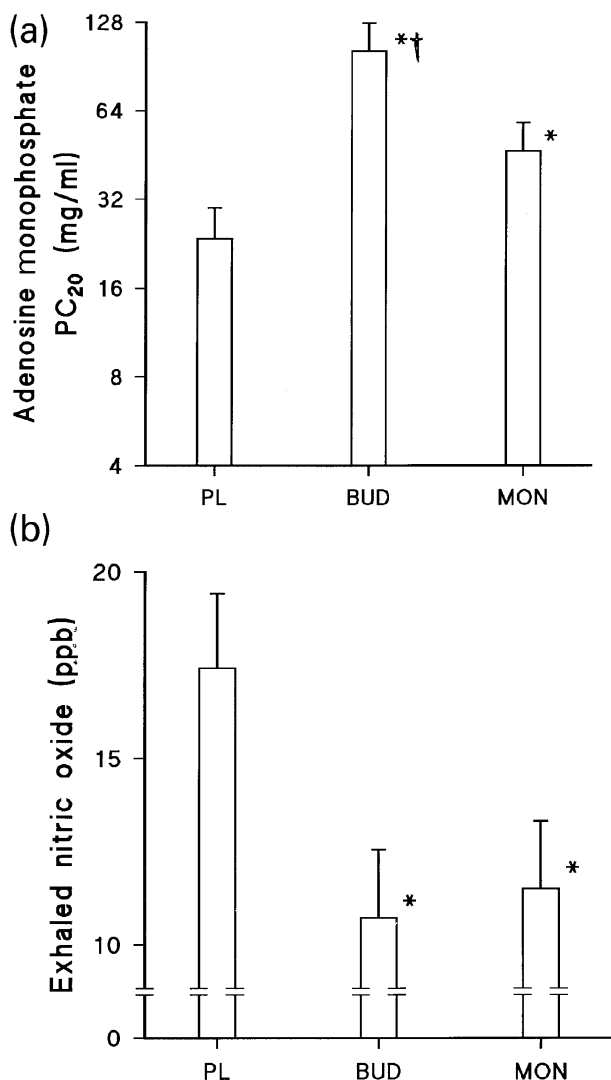


Fig. 2 (a) Geometric mean with S.E.M. for adenosine monophosphate bronchial challenge PC₂₀ for run-in placebo (PL), inhaled and intranasal budesonide (BUD) and oral montelukast (MON). *Significant ($P < 0.05$) difference between active treatment and placebo; †significant difference between active treatments. The scale for PC₂₀ is shown on a log₂ scale to depict doubling doses. (b) Means with standard error of mean for exhaled nitric oxide (p.p.b.). Legend as (a).

PC₂₀ were log-transformed in order to normalize their distribution prior to analysis. Effects on exhaled and nasal NO were considered to be secondary endpoints of main interest. On each day a total seasonal allergic rhinitis symptom score was calculated as the sum of each patient's individual nose, eye and throat symptom scores. Daily tree, grass and weed pollen count data were summed to provide a daily pollen score for each day of the study. For all domiciliary diary and pollen data, mean values for the 7-day placebo run-in and washout periods

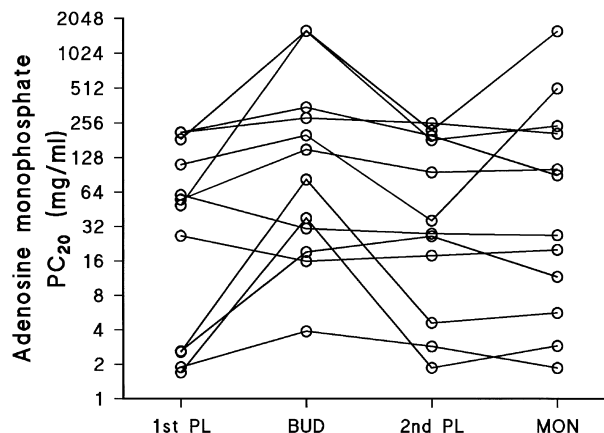


Fig. 3 Scatter-plot showing individual response for adenosine monophosphate bronchial challenge PC₂₀ for run-in placebo (1st placebo), inhaled and intranasal budesonide (BUD), washout placebo (2nd placebo) and oral montelukast (MON).

and for the last 7 days of active treatment period were analysed.

Overall comparisons between active treatments and placebos were made by multifactorial analysis of variance (MANOVA) using subject, treatment and period as factors. Pollen levels were factored into the analysis as a covariate in order to account for any possible influence of variation in pollen levels during the study. This was followed by Bonferroni multiple-range testing (set at 95% confidence interval (CI)) in order to obviate multiple pair-wise comparisons. Consequently comparisons are only denoted as being significant ($P < 0.05$) or not significant in order not to confound the α error.

Results

There were no significant carryover effects between the first (run-in) and second (washout) placebo values in sequence with any of the measurements (Table 1). Consequently all comparisons were made with reference to the run-in placebo.

Lower airway efficacy markers

There was a significant difference between both treatments and placebo and also a significant difference between active treatments for effects on adenosine monophosphate bronchial challenge—the primary endpoint (Fig. 2). Geometric mean differences (95% CI for difference) were 6.4-fold (2.2–18.6) for placebo vs. budesonide, 2.9-fold (1.0–8.4) for placebo vs. montelukast, and 2.1-fold (1.1–4.5) for budesonide vs. montelukast. There was a great deal of interindividual variation in the response to leukotriene receptor antagonists (Fig. 3). For

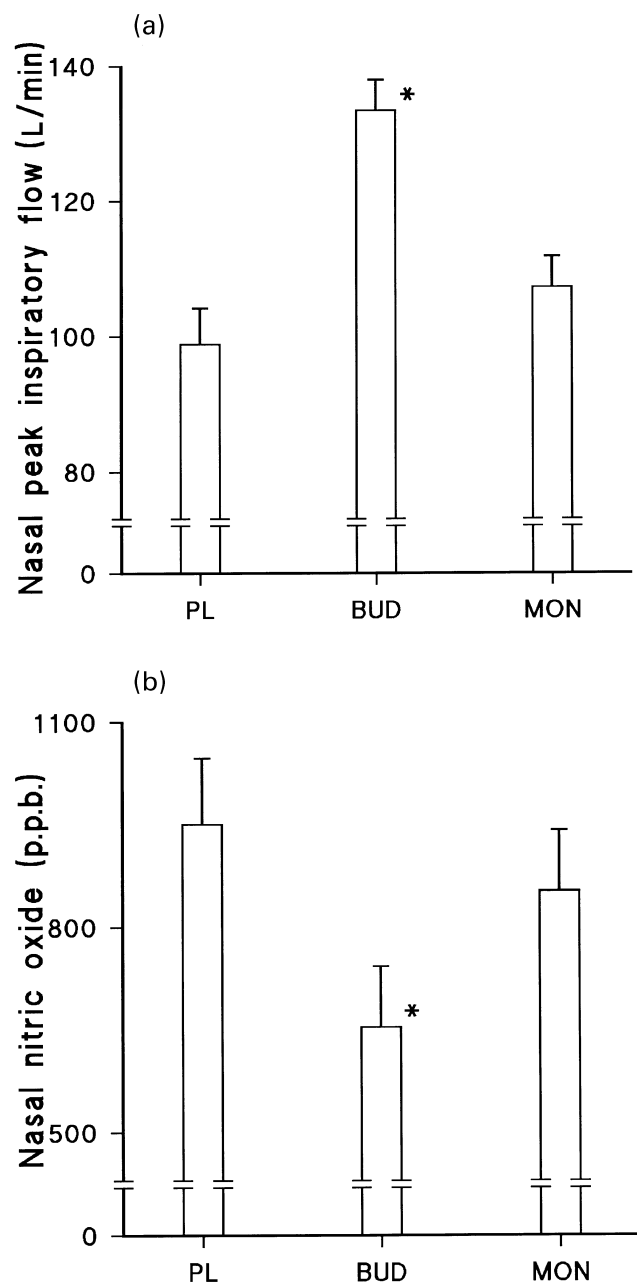


Fig. 4 (a) Means for morning nasal peak inspiratory flow rate. Legend as Fig. 2a. (b) Means for nasal nitric oxide. Legend as Fig. 2a.

exhaled NO (Fig. 2) there were also significant differences (95% CI for difference) between placebo vs. montelukast, 7.9 p.p.b. (0.8–15.6), and placebo vs. budesonide, 8.7 p.p.b. (0.9–16.4). For spirometry data, asthma symptom scores, peak expiratory flow, and rescue agonist usage there were similar numerical trends for improvements with both budesonide and montelukast compared with placebo, although these differences were not statistically significant (Table 2).

Upper airway efficacy markers

For nasal NO (Fig. 4) there was a significant difference (95% CI for difference) for placebo vs. budesonide, 369.3 p.p.b. (15.4–723.2), but not with montelukast. Likewise for domiciliary morning nasal peak flow there was a significant difference with placebo vs. budesonide, 36.8 L/mm (15.9–57.5), but not with montelukast. Both active treatments produced significant effects on eye symptoms and total seasonal allergic rhinitis symptoms (i.e. nose, eye and throat symptoms) compared with placebo, whilst only budesonide significantly affected nasal symptoms and daily activity scores (Table 2).

Discussion

We have shown that in patients with concomitant seasonal allergic rhinitis and asthma the use of oral montelukast or inhaled plus intranasal budesonide both exhibited significant effects on markers of lower airway inflammation (adenosine monophosphate bronchial challenge and exhaled NO), whilst only inhaled plus intranasal budesonide therapy showed significant improvements on upper airway parameters (nasal NO and nasal peak inspiratory flow rate). Both active treatments exhibited significant improvements in total seasonal allergic rhinitis symptoms and on eye symptoms alone, whilst only budesonide improved nasal symptoms and daily activity scores.

The results of the present study are similar to those of Pullerits *et al* [16] who showed that treatment for 50 days with intranasal beclomethasone dipropionate 200 µg daily but not oral zafirlukast 20 mg twice daily, had significant effects on nasal symptoms and nasal biopsy eosinophils, compared with placebo, in patients with seasonal allergy. Our patients had relatively mild allergic rhinitis and the study was not powered on nasal symptoms as such. Nonetheless, it was possible to show significant effects of corticosteroid treatment on subjective and objective markers of allergic rhinitis in our patients. The current results showing lower airway anti-inflammatory activity with montelukast as monotherapy are consistent with bronchial biopsy data from Nakamura *et al* [17], where pranlukast produced a significant reduction in numbers of T cells, eosinophils, mast cells as well as a concomitant fall in methacholine hyperreactivity after allergen challenge.

Our results with exhaled NO are in keeping with those of Jatakanon *et al* [18], who also showed suppression of exhaled NO production at a dose of 400 µg/day of budesonide Turbuhaler. There are also data to suggest that leukotriene receptor antagonists reduce exhaled NO when given in addition to inhaled corticosteroids [19]. Bisgaard *et al* [20] have shown that in asthmatic children, half of

whom were receiving inhaled corticosteroids, the addition of montelukast for 2 weeks resulted in suppression of exhaled NO which was further suppressed when inhaled 200 µg budesonide was added irrespective of their usual inhaled corticosteroid dose. Regarding nasal NO production, studies have demonstrated suppression with intranasal corticosteroids [21].

A recent study showed significant anti-inflammatory effects, in terms of methacholine bronchial challenge and sputum eosinophil counts, after 4 weeks with pranlukast [22], which is in keeping with *in vitro* data showing leukotriene receptor antagonists to increase rates of eosinophil apoptosis [23]. However, the present study is the first to compare the effects of a leukotriene antagonist and an inhaled steroid using adenosine monophosphate bronchial challenge.

We deliberately chose to perform all of the laboratory measurements in this study at trough. This was done in order to investigate the effect of the airways when they are their most vulnerable, i.e. prior to the next dose at the end of the 24-h dosing interval. It was important for us to evaluate once daily therapy as most seasonal allergic rhinitis is given only once daily and patients with mild asthma are adequately treated with once daily inhaled corticosteroids. Montelukast and budesonide were chosen as they are the only once daily medication in their class of therapy. Previous studies showed significant protection against exercise-induced bronchoconstriction with once daily budesonide and montelukast at trough [24–26].

Adenosine monophosphate bronchial challenge has been shown to be more sensitive than methacholine in terms of effects of inhaled corticosteroids [27]. It also reaches a maximum response within a few days [28]. Bronchial challenge testing with adenosine monophosphate is also considered to be more representative than methacholine of real-life asthmatic responses [7], and is an indirect stimulus like allergen, cold air or exercise. However, as leukotrienes are one of the inflammatory mediators released from mast cells, blocking these mediators with a leukotriene receptor antagonist may improve the response to adenosine monophosphate without controlling inflammation. However, in this study there was also suppression of exhaled NO, and therefore it is probable that montelukast exhibited a beneficial effect on airway inflammation. Furthermore, the effect of montelukast (2.9-fold difference) was less than that of budesonide (6.4-fold difference). Which is in keeping with a study comparing fluticasone and zafirlukast in terms of histamine bronchial challenge testing which showed significantly greater broncho-protection with the inhaled corticosteroid [29].

Although it was not possible to perform any subgroup analysis in our study, it can be seen from Fig. 3 that there is

a great deal of interindividual variation in the response to therapy with leukotriene receptor antagonists. Some patients responded equally well with both the inhaled plus intranasal corticosteroid and the leukotriene receptor antagonist. Others subjects had virtually no response with montelukast compared with budesonide. Previous authors have also shown a divergence in response with leukotriene modifying medication [30], which may be a result of genetic polymorphisms [31].

We elected to study patients with mild persistent asthma, as leukotriene antagonists and once daily budesonide are only recommended as monotherapy in such patients. As a result our patients had near normal spirometry with a mean FEV₁ of 91% predicted and we were therefore not surprised to see little improvement in lung function. Likewise, with asthma symptom scoring we did not find a significant improvement with either treatment, although there was a numerical trend with topical budesonide having better symptom control and less β₂ agonist use than montelukast or placebo. Our study was powered on bronchial challenge testing, but had we investigated more severe patients or used greater numbers of patients these differences may have been significant.

As there is significant overlap in the pathophysiology of allergic rhinitis and asthma, it is important to optimize nasal inflammation when treating patients, in order to optimize control of lower airway inflammation. Studies have shown that in patients with allergic rhinitis and concomitant mild asthma, intranasal corticosteroids as monotherapy prevent the increase in airway hyperreactivity during the pollen season [32,33] and improve asthmatic symptoms [34]. In our study, the greater anti-asthmatic efficacy of topical budesonide may be, in part, due to the greater control of nasal inflammation, although we did not evaluate the effects of inhaled or intranasal budesonide alone.

Although bronchial challenge testing and nasal peak inspiratory flow were the only parameters to show significantly greater efficacy with the corticosteroid than the leukotriene antagonist, there was a similar numerical trend for other upper and lower airway markers, and it is conceivable that such differences would have become significant with a larger sample. Previous studies have also shown low-dose inhaled corticosteroids to exhibit superior control of symptoms and lung function than leukotriene antagonists as monotherapy [35]. This is probably due to the greater anti-inflammatory potency of corticosteroids, which have a broad spectrum of activity on the inflammatory cascade rather than on one of the inflammatory mediators.

In conclusion, once daily montelukast and once daily budesonide exhibited significant effects on adenosine monophosphate challenge and exhaled NO, as well as on

total seasonal allergic rhinitis symptom scores. Budesonide exhibited significantly greater effects than montelukast on adenosine monophosphate hyperreactivity, whilst nasal NO and nasal peak flow were significantly improved by budesonide but not by montelukast. Combined therapy with once daily inhaled and intranasal corticosteroids may have potential advantages as first-line treatment for patients with seasonal allergic rhinitis and asthma. Further longer-term studies are now required to determine whether combination therapy with oral leukotriene and histamine receptor antagonists might be likely to match the upper airway effects of combination therapy with inhaled and intranasal corticosteroids. Also, as the lower airway effects of an oral leukotriene receptor antagonist and inhaled corticosteroid are additive [36], it would be interesting to evaluate any additive effect on the upper airway.

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