Effects of single or combined histamine H$_1$-receptor and leukotriene CysLT$_1$-receptor antagonism on nasal adenosine monophosphate challenge in persistent allergic rhinitis

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Background
The effects of single or combined histamine H$_1$-receptor and leukotriene CysLT$_1$-receptor antagonism on nasal adenosine monophosphate (AMP) challenge in allergic rhinitis are unknown.

Objective
We elected to study the effects of usual clinically recommended doses of fexofenadine (FEX), montelukast (ML) and FEX + ML combination, compared with placebo (PL), on nasal AMP challenge in patients with persistent allergic rhinitis.

Methods
Twelve patients with persistent allergic rhinitis (all skin prick positive to house dust mite) were randomized in a double-blind cross-over fashion to receive for 1 week either FEX 180 mg, ML 10 mg, FEX 180 mg + ML 10 mg combination, or PL, with nasal AMP challenge performed 12 h after dosing. There was a 1-week washout period between each randomized treatment. The primary outcome measure was the maximum percentage peak nasal inspiratory flow (PNIF) fall from baseline after nasal AMP challenge vs. PL, 48, with FEX, 37 (95% confidence interval for difference 2, 20); ML, 35 (4, 22); and FEX + ML, 32 (7, 24). The AUC (%.min) was also significantly attenuated vs. PL, 1893, with FEX, 1306 (30, 1143); ML, 1246 (214, 1078); and FEX + ML, 1153 (251, 1227). There were no significant differences for FEX vs. ML vs. FEX + ML comparing either the maximum or AUC response. The total nasal symptom score (out of 12) was also significantly improved vs. PL, 3.3, with FEX, 2.1 (0.3, 2.0); ML, 2.0 (0.5, 1.9); and FEX + ML, 2.5 (0.1, 1.4).
Introduction
Nasal provocation is widely used to assess the effectiveness of therapy in the upper airway [1, 2]. Nasal challenge with adenosine monophosphate (AMP) is a novel method of assessing upper airway hyperresponsiveness [3], which is a feature of allergic rhinitis [1]. Although the effects of various pharmacotherapies on bronchial AMP challenge have been thoroughly evaluated [4], there is a paucity of corresponding studies on nasal AMP challenge. This is particularly relevant, as bronchial AMP challenge has been shown to be sensitive in reflecting the underlying inflammatory process [4–8]. AMP acts indirectly by triggering primed mast cells to release mediators such as histamine, cysteinyl leukotrienes and prostaglandins [9].

Data relating to the combined effects of histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists on nasal symptoms in allergic rhinitis offer conflicting results. One study of patients with seasonal allergic rhinitis showed that although the combination of loratadine and montelukast (ML) improved the primary outcome of day-time symptoms, each drug alone was no better than placebo (PL) [10]. In contrast, in another larger study of patients with seasonal allergic rhinitis, both drugs alone improved day-time symptoms with no further additional benefit from the combination [11].

Although histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists have been found to attenuate the response to bronchial AMP challenge [4], their effects on nasal AMP challenge have yet to be evaluated. We therefore elected to study the effects of usual clinically recommended doses of fexofenadine (FEX), ML, and FEX + ML combination, on nasal AMP challenge in patients with persistent allergic rhinitis.

Patients and methods
Eligible patients were required to have a history of persistent allergic rhinitis [12] and a positive response to nasal AMP challenge. Patients with concomitant asthma (either with a history of asthma or on treatment for asthma) were excluded from the study. Patients were required to demonstrate sensitization on skin prick testing to house dust mite (n = 12), and to at least one other common aeroallergen such as cat (n = 5), dog (n = 2), aspergillus (n = 1), feather (n = 1), grass (n = 8), tree (n = 1), and weed (n = 3), using a standard protocol (Bencard Testing Solutions, Welwyn Garden City, UK). Patients were also required to have stable disease and to have been maintained on unchanging therapy without recent exacerbation requiring either oral corticosteroids or antibiotics within the past 3 months. Significant nasal septal deviation and the presence of nasal polyposis were excluded by nasal endoscopy using a rigid 30° Hopkins® Telescope (Karl Storz Endoscopy Ltd, Slough, UK). Patients received appropriate instructions and were required to demonstrate good technique in the use of the Mini-Wright® peak nasal inspiratory flow (PNIF) meter (Clement Clarke International Ltd, Harlow, UK), which was further reemphasized and reassessed, at each study visit.

Nasal challenge was performed as previously described [13] using a single 400 mg ml⁻¹ dose of AMP with measurements of PNIF at 1.5, 5, 10, 15, 20, 30, 40, 50, and 60 min. A positive response to nasal AMP challenge at initial screening was a prerequisite as defined by a maximal fall in PNIF of at least 20% from baseline. In addition, forced nasal inspiratory volume in 1 s (FNIV₁) was recorded using a MicroLoop® meter (Micro Medical Ltd, Rochester, UK) prior to AMP challenge. All patients gave informed consent for participation in the study, which was approved by the Tayside Committee on Medical Research Ethics.

Patients were required to undergo a 1-week run-in period prior to their screening visit where they stopped all their usual therapy for allergic rhinitis such as histamine H₁-receptor antagonists (n = 11) and intranasal corticosteroids (n = 5). Eligible patients were randomised at screening to receive for 1 week, either FEX 180 mg (Telfast®; Aventis Pharma Ltd, West Malling, UK), ML 10 mg (Singulair®; Merck Sharp & Dohme Ltd, Hoddesdon, UK), FEX 180 mg + ML 10 mg combination, or PL. All tablets were placed in a single identical capsule in order to double-blind the study and were taken once daily at 22.00 h. Patients attended each of their study visits at 10.00 h and underwent nasal AMP challenge 12 h following their last dose of medication. There was a 1-week washout period between each randomized treatment where patients received PL once daily at 22.00 h. Throughout the study, patients also kept a record of their daily nasal symptoms using a diary card based on a four-point scale (0 for no symp-
toms and 3 for severe symptoms) for blocked nose, runny nose, itchy nose, and sneezing. The average value from the last 5 days of each treatment was used for analysis.

**Expression of results and statistical analysis**

The maximum percentage PNIF fall from baseline was the primary outcome measure used to power the study at 80%, in order to detect a 25% difference between active treatments vs. PL, with a sample size of 12 completed patients per protocol in a cross-over design. Secondary outcome measures included the area under the 60-min time–response curve (AUC) and nasal symptoms. An overall analysis of variance followed by multiple-range testing with Bonferroni correction set at 95% confidence intervals (CI) was performed using Statgraphics® statistical software package (STSC Software Publishing Group, Rockville, MD, USA). Results were quoted as being either significant ($P < 0.05$) or not, in order not to confound the overall $\alpha$-error set at 0.05 (two-tailed).

**Results**

Twelve patients (four men and eight women) with mean (standard error of mean) age of 42 (4) years were enrolled and all completed the study. Prechallenge values for both FNI\textsubscript{v} (l) and PNIF (l min\textsuperscript{-1}), respectively, were not significantly different comparing FEX, 1.97 (0.12) and 147 (8) vs. ML, 1.88 (0.12) and 135 (9) vs. FEX + ML, 1.91 (0.16) and 131 (11) vs. PL, 1.82 (0.11) and 130 (8).

Data for nasal AMP challenge are depicted in Figures 1, 2, and 3. The intraindividual coefficient of variation for the nasal AMP challenge comparing initial screening vs. PL was 5.1%, with mean values for the maximum percentage PNIF fall from baseline of 49 (4) vs. 48 (3). There was significant attenuation ($P < 0.05$) of the mean maximum percentage PNIF fall from base-
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line after nasal AMP challenge vs. PL, 48 (3), with FEX, 37 (3), 95% CI for difference (2, 20); ML, 35 (2), (4, 22); and FEX + ML, 32 (3), (7, 24). The AUC (%.min) was also significantly attenuated (P < 0.05) vs. PL, 1893 (158), with FEX, 1306 (155), (30, 1143); ML, 1246 (127), (214, 1078); and FEX + ML, 1153 (186), (251, 1227). There were no significant differences for FEX vs. ML vs. FEX + ML comparing either the maximum or AUC response.

The total nasal symptom score (out of 12) was also significantly improved (P < 0.05) vs. PL, 3.3 (0.5), with FEX, 2.1 (0.6), (0.3, 2.0); ML, 2.0 (0.5), (0.5, 1.9); and FEX + ML, 2.5 (0.5), (0.1, 1.4). Nasal blockage (out of 3) was also significantly improved (P < 0.05) with FEX, 0.7 (0.2), (0.1, 1.1); ML, 0.8 (0.2), (0.1, 0.8); and FEX + ML, 0.9 (0.1), (0.1, 0.7), vs. PL, 1.3 (0.2).

Discussion

Our results showed that either FEX or ML as monotherapy attenuated the response to nasal AMP challenge and improved nasal symptoms, although there were no added effects conferred by the histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists in combination.

To the best of our knowledge, this is the first study to evaluate the effects of histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists either alone or in combination on nasal AMP challenge. Bronchial AMP challenge has been shown to be a sensitive surrogate for both the underlying inflammatory process and the response to pharmacotherapy in allergic asthma [4]. PNIF has been shown to be a more sensitive measure than either acoustic rhinometry or rhinomanometry in evaluating responses related to upper airway challenge [14]. We measured both PNIF and FNIV₁ prior to nasal AMP challenge, which were not significantly different for comparison between the randomized treatments. We have previously reported in patients with allergic rhinitis that both parameters have a low degree of intraindividual variability for repeated measurements, with coefficient of variation values of 8% and 4%, respectively, for PNIF and FNIV₁ [15].

Histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists when used as either monotherapy or add-on therapy to inhaled corticosteroids have been shown to attenuate the response to AMP in the lower airway. It is perhaps not surprising to find that the effects on AMP response are also mirrored in the upper airway by both histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists, further reinforcing the concept of the unified allergic airway [12, 16]. Our results on nasal AMP challenge are in keeping with previous data showing attenuation of nasal mannitol challenge by desloratadine and ML [17]. This similarity can be explained by both AMP and mannitol acting as indirect proinflammatory stimuli, the former causing primed mast cells to release mediators [9] while the latter exerts its effects as a hyperosmolar stimulus [18, 19].

There are conflicting data regarding the possibility of additive responses with challenge models using histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists. In the lower airway, using allergen challenge, additivity of response was seen with loratadine and zafirlukast, which was statistically significant but clinically irrelevant, compared with each agent alone [20]. However, for the cutaneous response to allergen, no such additivity of response was seen using FEX and ML, with the latter having no effect compared with PL [21].

The role of histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists in the upper airway in relation to nasal symptoms has also produced conflicting results. A study of 1302 patients with seasonal allergic rhinitis showed improvements of both day-time and night-time nasal symptoms following treatment with either loratadine or ML [22]. Another study of 460 patients with seasonal allergic rhinitis showed that neither loratadine and ML, when used on their own, conferred any benefit in terms of improving day-time nasal symptoms [10]. Nevertheless, in the same study, when the two drugs were combined, day-time nasal symptoms were significantly improved. Nayak et al. showed that both drugs when used alone improved day-time nasal symptoms, but the combination of both loratadine and ML did not confer additional benefit, in a study of 907 patients with seasonal allergic rhinitis [11]. A study of 62 patients with seasonal allergic rhinitis found the combination of loratadine and ML was no more effective than ML alone on day-time or night-time symptoms [23]. In the same study, epithelial eosinophils from nasal biopsy were lower with ML alone than with the combination, which is difficult to explain. In comparison with intranasal corticosteroids, the use of oral combined histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists has been shown to be equal in two studies and inferior in another, for effects on nasal symptoms [23–25].

Our results on nasal AMP challenge and symptoms are in keeping with the study by Nayak et al. and are supported by other data on seasonal allergic rhinitis, where adding ML to cetirizine was not significantly different from the effects of cetirizine alone on nasal symptoms. The improvement in nasal blockage symptoms with histamine H₁-receptor and leukotriene CysLT₁-receptor antagonists in our study is in keeping
with previous data showing that nasal obstruction is a process mediated by histamine and cysteinyl leukotrienes [26, 27]. However, although our patients had persistent allergic rhinitis, their overall symptoms were relatively mild, suggesting that further studies are required to evaluate putative additive response with combined histamine H<sub>4</sub>-receptor and leukotriene CysLT<sub>1</sub>-receptor antagonists in more severe patients. Nonetheless, even in relatively mild patients we were able to show a significant difference between active treatments and PL, which were in the same direction as to the effects on nasal AMP challenge. It is, however, conceivable that if we had selected, for example, patients with more severe symptoms, this might have identified a greater potential for additivity of response. Perhaps the putative benefits of such combination therapy may become evident only when looking at concomitant effects on asthma control in patients who have concomitant allergic rhinitis.

In summary, FEX and ML as monotherapy significantly attenuated the response to nasal AMP challenge and improved nasal symptoms, with no additional benefit conferred by combination therapy.

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