

A placebo-controlled evaluation of butterbur and fexofenadine on objective and subjective outcomes in perennial allergic rhinitis

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Summary

Background There are presently no placebo-controlled data regarding the effects of butterbur (BB) on subjective and objective outcomes in patients with perennial allergic rhinitis.

Objective We performed a placebo-controlled evaluation of the effects of BB and fexofenadine (FEX) on subjective and objective outcomes in patients with perennial allergic rhinitis.

Methods Sixteen patients with perennial allergic rhinitis and house dust mite sensitization were randomized in double-blind cross-over fashion to receive for 1 week either BB 50 mg twice daily, FEX 180 mg once daily and placebo (PL) once daily, or PL twice daily. The peak nasal inspiratory flow (PNIF) response to adenosine monophosphate (AMP) challenge administered as a single 400 mg/mL dose was measured over a 60-min period after challenge, and domiciliary total nasal symptom score was recorded.

Results Pre-challenge values for mean $\pm$ SEM PNIF (L/min) were not significantly different comparing all groups; BB (138 ± 8), FEX (140 ± 9), and PL (138 ± 8). The maximum % PNIF fall from baseline after nasal AMP challenge was significantly attenuated ($P < 0.05$) compared to PL (46 ± 3), with BB (34 ± 3) and FEX (39 ± 3). The area under the 60-min time–response curve (%.min) was also significantly attenuated ($P < 0.05$) compared to PL (1734 ± 156), with BB (1052 ± 258) and FEX (1194 ± 161). There was also a significant reduction ($P < 0.05$) in total nasal symptom score with BB (1.8 ± 0.4) and FEX (1.8 ± 0.4), compared to PL (2.8 ± 0.5). There were no significant differences between BB and FEX for any outcomes.

Conclusion BB and FEX, in comparison to PL, were equally effective in attenuating the nasal response to AMP and in improving nasal symptoms, highlighting a potential role for BB in the treatment of allergic rhinitis.

Keywords adenosine monophosphate, butterbur, fexofenadine, H₁-antihistamine, nasal challenge, peak nasal inspiratory flow, perennial allergic rhinitis, petasin, *petasites hybridus*

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Introduction

There has been much interest surrounding a herbal remedy, butterbur (BB) or *Petasites hybridus*, both in the clinical and research arena. The active ingredient of BB has been identified as petasin which produces an inhibitory effect on cysteinyl leukotrienes and histamine synthesis [1–5]. Although BB has been shown in a non-placebo-controlled study to be equal in its effects on improving subjective nasal symptoms compared to a H₁-antihistamine, cetirizine [6], there are presently no placebo-controlled data assessing objective or subjective outcomes with these treatments.

Measurement of the bronchial response to indirect stimuli provocation such as adenosine monophosphate (AMP) is a well-validated method of assessing efficacy of anti-inflammatory therapy, and has been shown to better reflect the un-

derlying inflammatory process [7]. H₁-antihistamine and leukotriene receptor antagonist are known to attenuate the response to AMP bronchial challenge [8, 9]. However, the effects of mediator antagonism on nasal AMP challenge in the upper airway have not been well-evaluated. In a previous study, we showed that BB compared to placebo (PL) significantly attenuated the response to nasal AMP challenge in patients with seasonal allergic rhinitis, although no assessment of nasal symptoms were made [10]. We therefore elected to evaluate the effects of BB and fexofenadine (FEX) in comparison to PL on the objective outcome of nasal responsiveness to AMP challenge and on the subjective outcome of nasal symptoms.

Methods

Patients

Eligible patients with a history of perennial allergic rhinitis were recruited from our database. None had received a course of oral corticosteroids or antibiotics over a period of at least 3

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months. All patients were required to exhibit a positive reaction to house dust mite on skin prick testing. Patients were also required to demonstrate a positive response to nasal AMP challenge at initial screening as defined by a maximal fall in peak nasal inspiratory flow (PNIF) of at least 20% from baseline. The study was conducted out of the pollen season in order to obviate any potential confounding effects in patients who were skin prick positive to pollen. All patients gave informed consent and the study was approved by the Tayside Committee on Medical Research Ethics.

Study design

The study flow diagram is shown in Fig. 1. The study was conducted in a randomized, double-blind, placebo-controlled, cross-over fashion. Patients had their usual allergic rhinitis therapy including H₁-antihistamine and intranasal corticosteroids stopped for a 1-week washout period prior to the initial screening visit and throughout the entire study period. Patients were randomized to receive for 1 week either BB 50 mg (Petaforce[®], Bioforce Ltd, Irvine, UK) twice daily (08:00 and 22:00 hours), FEX 180 mg (Telfast[®], Aventis Pharma Ltd, West Malling, UK) once daily (22:00 hours) and PL once daily (08:00 hours), or PL twice daily (08:00 and 22:00 hours). There was a 1-week washout period between each randomized treatment. All tablets were encapsulated and were identical in external physical appearance. Patients took the last dose of study capsule at 08:00 hours and attended the department at 10:00 hours the same day.

Measurements

Skin prick testing Skin prick testing was performed following a standard protocol (Bencard Testing Solutions, Welwyn Garden City, UK) using extracts including house dust mite, cat, dog, grass, tree, and weed pollen in addition to a negative control. Results were read after 15 min, a positive reaction being defined as a weal diameter of at least 3 mm greater than the negative control.

Nasal endoscopy A significant degree of nasal septal deviation of more than 50% and the presence of nasal

polypsis were excluded by nasal endoscopy using a rigid 30° Hopkins[®] Telescope (Karl Storz Endoscopy Ltd, Slough, UK).

PNIF All patients received appropriate instructions and were required to demonstrate good technique in recording their PNIF using the In-Check[®] PNIF meter (Clement Clarke International Ltd, Harlow, UK) at the initial screening visit. The technique was then further reassessed and reinforced, prior to each nasal AMP challenge, at each study visit.

Nasal AMP challenge Nasal AMP challenge was performed as previously described [10]. In brief, patients received a single dose of AMP (400 mg/mL) administered via a pump actuator spray device as two squirts per nostril. The response to nasal AMP challenge was recorded with measurements of PNIF at 1.5, 5, 10, 15, 20, 30, 40, 50, and 60 min.

Nasal symptom score Patients recorded their nasal symptoms based on a 4-point scoring scale (0 indicating no symptoms and 3 indicating severe symptoms) for runny nose, stuffy nose, itchy nose and sneezing, using a diary card. A total nasal symptom score (out of 12) was then calculated and the average of the last 5 days of each randomized treatment was used for analysis.

Statistical analysis

The study was powered at 80% with α -error set at 0.05 (two-tailed) in order to detect a 25% difference in the maximum % PNIF fall from baseline (the primary outcome) between active treatments and PL, with a sample size of 16 completed patients in a cross-over design. We also calculated the area under the 60-min time-response curve (AUC) as a secondary outcome. An overall analysis of variance followed by multiple-range testing with Bonferroni correction set at 95% confidence interval (CI) was performed using Statgraphics[®] statistical software package (STSC Software Publishing Group, Rockville, MD, USA). In order not to confound the overall α -error, results were quoted as being either significant ($P < 0.05$) or not.

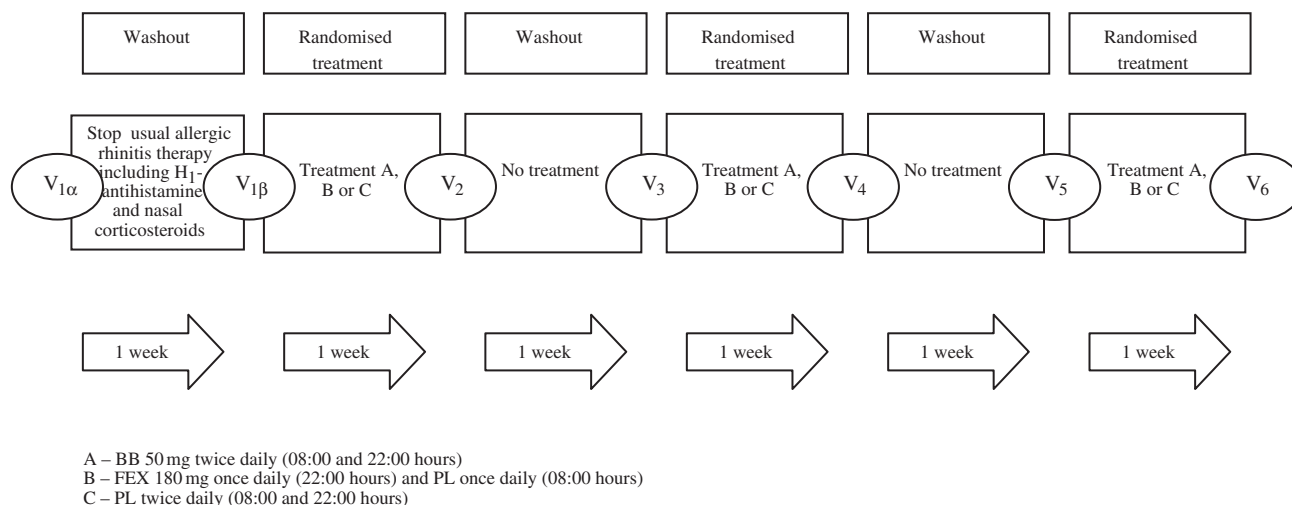


Fig. 1. Study flow diagram depicting washout and randomized treatment periods, with study visits (V₁–V₆).

Results

Patients

Patient demographic data are shown in Table 1. Sixteen patients (seven male patients and nine female patients) with mean $\pm$ standard error of mean age of 43 ± 3 years were enrolled and all completed the study per protocol.

Nasal AMP challenge

Nasal AMP challenge data are shown in Figs 2 and 3. Pre-challenge values for mean PNIF (L/min) were not significantly

different comparing all groups: BB (138 ± 8), FEX (140 ± 9), and PL (138 ± 8). There was no significant difference in the maximum % PNIF fall from baseline comparing screening (46 ± 5) and PL (46 ± 3). The intra-individual coefficient of variation for the reproducibility of the nasal AMP challenge was 1.1%. The maximum % PNIF fall from baseline after nasal AMP challenge was significantly attenuated ($P < 0.05$) compared to PL (46 ± 3), with BB (34 ± 3): 95% CI for difference (5–20), and FEX (39 ± 3): 95% CI for difference (1–15). The AUC (%.min) was also significantly attenuated ($P < 0.05$) compared to PL (1734 ± 156), with BB (1052 ± 258): 95% CI for difference (94–1270), and FEX (1194 ± 161): 95% CI for difference (66–1015). There were no significant differences between BB and FEX for either the maximum or AUC response.

Nasal symptom score

The total nasal symptom score (out of 12) was significantly improved ($P < 0.05$) compared to PL (2.8 ± 0.5), with BB (1.8 ± 0.4): 95% CI for difference (0.2–1.6), and FEX (1.8 ± 0.4): 95% CI for difference (0.1–1.7).

Discussion

Our results demonstrated that both BB and FEX were equally effective, compared to PL, in attenuating the nasal response to AMP challenge in addition to improving nasal symptoms in patients with perennial allergic rhinitis. This would be in keeping with our previous study of patients with grass pollen-sensitized seasonal allergic rhinitis, which also showed attenuation of the nasal AMP response by BB compared to PL [10]. Indeed, in our previous study in seasonal allergic rhinitis, there was attenuation of the maximum response to AMP by 30% with BB against PL, as compared to 26% attenuation in the present study. Moreover, our present findings are consistent with a non-placebo-controlled study comprising 125 patients with seasonal allergic rhinitis, which found BB to be equally as effective as cetirizine in

Table 1. Patient demographic details

Subject	Sex	Age (years)	SPP	Treatment
1	F	31	G, HDM	Chlorphenamine, beclomethasone
2	F	33	HDM, A, F	Mometasone
3	F	32	G, HDM, C	Desloratadine, budesonide
4	F	33	HDM, C	Loratadine
5	M	31	HDM, D	Cetirizine
6	M	60	G, HDM, C	Mometasone, loratadine
7	F	64	G, W, HDM	Loratadine
8	M	52	HDM, C	Desloratadine
9	M	48	G, HDM, D, C	Cetirizine
10	F	48	G, HDM	Loratadine
11	M	41	G, T, HDM, C	Loratadine
12	M	52	G, HDM	Cetirizine
13	F	23	G, T, W, HDM, D, C	Levocetirizine
14	F	36	HDM, D, C	Cetirizine
15	F	55	G, C, HDM	Cetirizine, budesonide
16	M	44	G, W, HDM	Loratadine

F, female; M, male; SPP, skin prick positive; G, grass; HDM, house dust mite; A, aspergillus; F, feather; C, cat; W, weed; D, dog; T, tree.

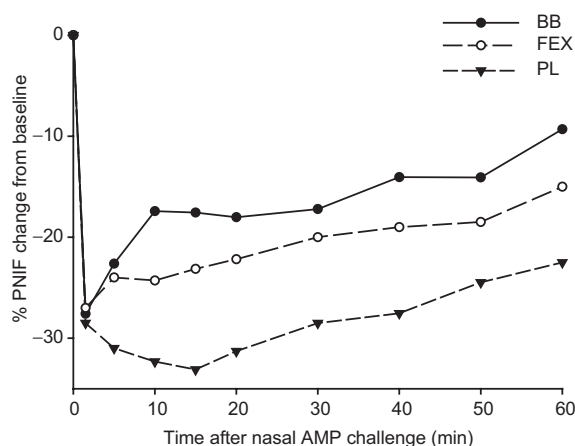


Fig. 2. Time-response profile over 60 min for % peak nasal inspiratory flow (PNIF) change from baseline after nasal adenosine monophosphate (AMP) challenge.

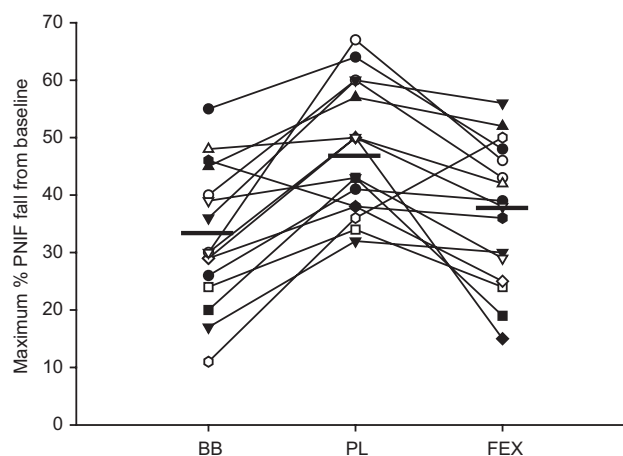


Fig. 3. Individual data for the maximum % peak nasal inspiratory flow (PNIF) fall from baseline showing butterbur (BB), placebo (PL) and fexofenadine (FEX) values, joined for each individual. Mean values for each of the randomized treatment are depicted by horizontal lines.

improving nasal symptoms [6]. To the best of our knowledge, this is the first placebo-controlled study, to assess both subjective and objective outcomes of BB in perennial allergic rhinitis together with a comparator group of a well established therapy such as FEX.

In order to avoid pollen sensitization being a confounding factor in some of our patients who were skin prick positive to grass pollen, we were careful to conduct our study out of the pollen season. Our patients had relatively mild perennial allergic rhinitis as reflected by their nasal symptoms. Nevertheless, we were able to demonstrate significant improvement in the total nasal symptom score with both BB and FEX compared to PL, although the magnitude of change was rather small. It is important to point out that our study was not powered on nasal symptoms, which was a secondary outcome measure. Nasal obstruction in the upper airway as measured by pre-challenge PNIF was not affected by both treatments, showing that altered nasal airway calibre was not an explanation for the reduction in nasal airway responsiveness to AMP challenge. PNIF has been shown to be as sensitive and as reproducible as acoustic rhinometry or rhinomanometry in detecting responses to nasal challenge in patients with allergic rhinitis [11]. AMP acts on A₂ receptors via priming of mucosal mast cells to release allergic inflammatory mediators such as histamine, cysteinyl leukotrienes, and prostaglandins [12], and when used as a nasal challenge has been found to be more sensitive compared to histamine in detecting response to intranasal corticosteroid therapy [13].

In vitro data provide some insight into the mechanism of action of both BB and FEX, whereby the former has been shown to inhibit the production of cysteinyl leukotrienes and histamine [1–5]. FEX on the other hand, has been shown to reduce intercellular adhesion molecule ICAM-1 expression from epithelial cells and fibroblasts [14], in addition to attenuating eosinophil-induced release of interleukin IL-8, ICAM-1 and granulocyte macrophage-colony stimulating factor from human nasal epithelial cells [15]. Tumour necrosis factor α -stimulated cell activation and the release of pro-inflammatory mediators such as β -glucuronidase and IL-6 from human lung macrophages along with exocytosis are known to be inhibited by FEX [16–18].

We understand the limitations of our study, which had a relatively short duration of treatment and was not powered on nasal symptoms. A much larger study in more severe patients would be indicated to evaluate symptoms and quality of life, as well as nasal biopsy or lavage tissue profile.

In summary, our results showed that BB and FEX, compared to PL, were equally effective in attenuating the nasal response to AMP and in improving nasal symptoms in patients with perennial allergic rhinitis.

Acknowledgements

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