

Original article

Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma

Background: Studies suggest that nasal treatment might influence lower airway symptoms and function in patients with comorbid rhinitis and asthma. We investigated the effect of intranasal, inhaled corticosteroid or the combination of both in patients with both pollen-induced rhinitis and asthma.

Methods: A total of 262 patients were randomized to 6 weeks' treatment with intranasal fluticasone propionate (INFP) 200 µg o.d., inhaled fluticasone propionate (IHFP) 250 µg b.i.d., their combination, or intranasal or inhaled placebo, in a multicentre, double-blind, parallel-group study. Treatment was started 2 weeks prior to the pollen season and patients recorded their nasal and bronchial symptoms twice daily. Before and after 4 and 6 weeks' treatment, the patients were assessed for lung function, methacholine responsiveness, and induced sputum cell counts.

Results: Intranasal fluticasone propionate significantly increased the percentages of patients reporting no nasal blockage, sneezing, or rhinorrhoea during the pollen season, compared with IHFP or intranasal or inhaled placebo. In contrast, only IHFP significantly improved morning peak-flow, forced expiratory volume in 1 second (FEV₁) and methacholine PD₂₀, and the seasonal increase in the sputum eosinophils and methacholine responsiveness.

Conclusions: In patients with pollen-induced rhinitis and asthma, the combination of intranasal and IHFP is needed to control the seasonal increase in nasal and asthmatic symptoms.

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Key words: fluticasone propionate; lung function; nasal symptoms; pollen-induced rhinitis and asthma; sputum eosinophils.

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Accepted for publication 10 January 2005

Rhinitis and asthma often occur as comorbid conditions. Epidemiological studies have demonstrated that about 60–80% of asthmatic individuals suffer from allergic rhinitis, and conversely approximately 20–40% of patients with allergic rhinitis suffer from asthma (1, 2). Pathophysiological studies have demonstrated several similarities in the nose and the bronchi, indicating that agents such as allergens and aspirin can trigger exacerbations of both asthma and rhinitis leading to inflammatory mucosal responses (3). Allergen challenge leads to an increase in mast cells, eosinophils, lymphocytes, and the expression of Th₂-profile proinflammatory cytokines in both allergic rhinitis and asthma (4, 5), and additionally, challenge in either the upper or lower airways of patients with rhinitis has been shown to increase eosinophilia in both the upper and lower airways, suggesting a link

between the upper and lower airways (6). Allergic rhinitis predisposes an individual to the development of asthma and/or to an increase in asthma symptoms (7, 8). There is also evidence suggesting appropriate treatment of allergic rhinitis to result in improvement of asthma (9–11). To date, however, no study has investigated the optimal treatment of pollen-induced rhinitis and asthma using intranasal and/or inhaled corticosteroids. Consequently, the aim of this study was to compare the effect of intranasal fluticasone propionate (INFP) and inhaled fluticasone propionate (IHFP) on nasal and bronchial symptoms, lung function and inflammatory cells of induced sputum in pollen-induced rhinitis and asthma. Fluticasone propionate was selected for study due to the virtual absence of systemic bioavailability with intranasal application (12, 13).

Methods

Patients

Patients aged 12 years and above, with an established clinical history of pollen-induced asthma and rhinitis during two of the last three seasons and positive skin test or radioallergosorbent test to relevant pollen allergens, were enrolled into the study. All had normal lung function, as indicated by prebronchodilator forced expiratory volume in 1 s (FEV₁) >80% of predicted value and FEV₁/VC >70%, and no signs or symptoms of asthma outside the pollen season. Patients who suffered from asthma and rhinitis because of allergens other than pollen, and those receiving chronic treatment with antiasthma medication or any immunosuppressants and/or immunotherapy over the last 3 years were excluded. The study population consisted of 69% never smokers, 15% previous smokers and 16% current smokers. Smoking status was equally distributed between treatment groups.

Study design

This was a randomized, double-blind, double dummy, placebo-controlled, parallel-group, multicentre study. The study involved four scheduled clinic visits. At the first visit, 4–6 weeks prior to the pollen season, patient demographics and medical history were recorded. Asthma and rhinitis symptoms and vital signs were assessed, lung function was measured, and methacholine bronchial challenge was performed. Induced sputum samples were collected. All eligible patients returned 2 weeks before the pollen season (visit 2) and following re-assessment as above, they were randomized to receive one of the following: (i) FP aqueous nasal spray 200 µg o.d., Flixonase® (INFP) + IHFP 250 µg b.i.d., Flixotide® via Diskus™ dry powder inhaler (IHFP), (ii) INFP + inhaled placebo, (iii) intranasal placebo + IHFP, or (iv) intranasal placebo + inhaled placebo. The patients were issued with diary cards and study medication. After treatment for 4 (visit 3) and 6 weeks (visit 4), the patients were re-assessed as before, and additionally for any adverse events and concurrent medication usage. At visit 3, methacholine bronchial challenge was performed and at visit 4 induced sputum samples were collected.

Patients were recruited between March 1998 and August 1999, and the study was completed in October 1999. The study was approved by the local Ethics Committees from the different centres and all patients gave written informed consent.

Outcome measures

Diary-card measures. Patients recorded morning and evening peak expiratory flow (PEF) during the entire study period, using mini-Wright peak flow meters (Clement Clarke International Ltd, Harlow, UK). Patients did this prior to taking their medication, recording the best of three measurements.

Additionally, patient records of daytime and night-time asthma and rhinitis symptoms (scored on a 4-point scale ranging from a score of 0 for no symptoms to 3 for incapacitating asthma/severe rhinitis symptoms) and use of rescue medication (inhaled salbutamol, intraocular levocabastine and oral acrivastine) were assessed.

Laboratory measures at clinic visits. Methacholine challenge: Bronchial provocation with inhaled methacholine was performed according to the recommendations of the European Respiratory Society (14). Following baseline FEV₁ measurement, the patient inhaled five breaths of nebulised control saline solution. The FEV₁ was recorded again after 90 s and the patient was

challenged at 5 min intervals with doubling concentrations of methacholine ranging from 0.125 to 32 mg/ml, until a 20% fall in postsaline FEV₁ was recorded. All results were expressed as cumulative inhaled dose causing a 20% fall in FEV₁ (PD₂₀) and given in µmol. The highest cumulative dose was equal to 14.7 µmol.

Sputum induction and processing: Sputum was induced and processed according to a standardized protocol (15). Prior to sputum induction, baseline FEV₁ was assessed and the patient inhaled 200 µg salbutamol. The patient then inhaled increasing concentrations (0.9, 3, 4 and 5%) of saline aerosol, until a sufficient sputum sample (250–300 mg) was obtained or until FEV₁ decreased by >20%. Sputum plugs were separated from saliva, weighed and dispersed with freshly prepared 10% dithiothreitol solution. The suspension was filtered through a 48 µm nylon mesh and centrifuged at 400 g for 10 min. The cell pellet was re-suspended in phosphate-buffered saline and analysed for cell viability and total cell count in a haemocytometer, and for differential cell counts in cytopspin slides after May-Grunwald Giemsa staining.

Sample size and randomizations

On the basis of variance (SD) for mean morning PEF of 45 l/min observed in previous studies, and assuming 90% power, a two-sided *t*-test for the pairwise comparison between placebo and IHFP, and a 5% significance level, it was planned to recruit 95 subjects per treatment arm. A randomization schedule was prepared using an in-house validated computer system by GlaxoSmithKline. The schedule was derived using a prespecified block size of 4, to ensure equal randomization between the treatment groups. The schedule was then used to prepare treatment packs and preprinted randomization envelopes for distribution to the study centres, with each centre receiving a number of complete blocks from the schedule. Investigators were instructed to allocate treatment packs to subjects sequentially, and to record the treatment number on the case record forms. Treatment packs were matched in terms of treatment presentation, and labelled only with a treatment number. The preprinted randomization envelopes were provided in case an emergency code-break was required, and all envelopes were tracked and returned at the end of the study. Access to the schedule was prohibited until the treatment allocation was broken prior to analysis, and investigators were not informed of any individual allocation to subjects until after the analysis was completed.

Statistical analysis

All analyses were performed on an intent-to-treat (ITT) population, comprising all subjects who took at least one dose of study medication. All statistical comparisons were conducted at the 5% significance level.

Data for the primary outcome measure of morning PEF and secondary variables, including evening PEF, percentage of symptom-free days and nights, symptom scores during the day and night and changes in FEV₁, were averaged over the 6 weeks of the study to produce average values on treatment. Differences between the treatment regimens were analysed using ANCOVA, with factors for cluster of centres, age, sex and mean value for each outcome measure during the last week of the run-in period. Differences between the treatments were assessed by including binary variables for the presence/absence of IHFP and the presence/absence of INFP in the randomized treatment. A factor for the interaction between the two formulations of FP was also

included. For the methacholine challenge data, the PD₂₀ values were logarithmically transformed prior to analysis and reported as geometric mean.

For the sputum counts, differences in change from baseline to end-point were analysed using a Wilcoxon rank sum test, and Hodges-Lehmann estimates of the median difference and associated 95% confidence interval were derived. For these data, the only comparisons performed were for the three active groups against intranasal or inhaled placebo.

Adverse events were coded using the Medical Indications, Diseases and Symptoms (MIDAS) dictionary, and summarized by the number reporting in each treatment group.

Results

Details of patient recruitment and withdrawals are shown in Fig. 1, and their demographic and baseline characteristics are presented in Table 1. Recruitment to the study was lower than planned, but the numbers recruited were still sufficient to have more than 80% power to find the assumed treatment difference. Of the 262 patients recruited into the study, 177 were allergic to grass-, 64 to birch-, 15 to ragweed-, and the remaining six to olive-, pecan- and parietaria-pollens.

Diary-card assessments

There was a higher morning PEF over time in patients treated with IHFP, and a decrease in patients treated

either with INFP alone or intranasal or inhaled placebo ($P < 0.001$) (adjusted mean values of 486.3, 480.5, 499.1, and 501.5 l/min, respectively, for patients treated with intranasal or inhaled placebo, INFP, IHFP, INFP + IHFP). The difference in PEF over the entire 6-weeks' treatment period between patients receiving any IHFP and patients receiving no IHFP was 13.1 l/min ($P < 0.001$). Patients on intranasal or inhaled placebo or INFP alone recorded the lowest morning PEF values at the height of the pollen season. The IHFP + INFP was found to be significantly better than intranasal or inhaled placebo or INFP alone, in improving morning PEF at the height of the pollen season ($P < 0.001$). Although evening PEF was not significantly altered from baseline at the height of the pollen season in any treatment group (adjusted mean values of 490.4, 487.0, 501.8, and 504.5 l/min, respectively, for patients treated with intranasal or inhaled placebo, INFP, IHFP, INFP + IHFP), there was an overall significantly greater improvement also for this parameter in patients receiving IHFP ($P < 0.001$).

The greatest number of wheeze-free days and nights at the height of the pollen season were recorded by patients treated with IHFP compared with patients on no IHFP treatment (data not shown; $P < 0.001$ for wheeze-free day, and $P = 0.006$ for wheeze-free nights).

The difference in asthma symptom-free nights over the entire 6-weeks' treatment period between patients

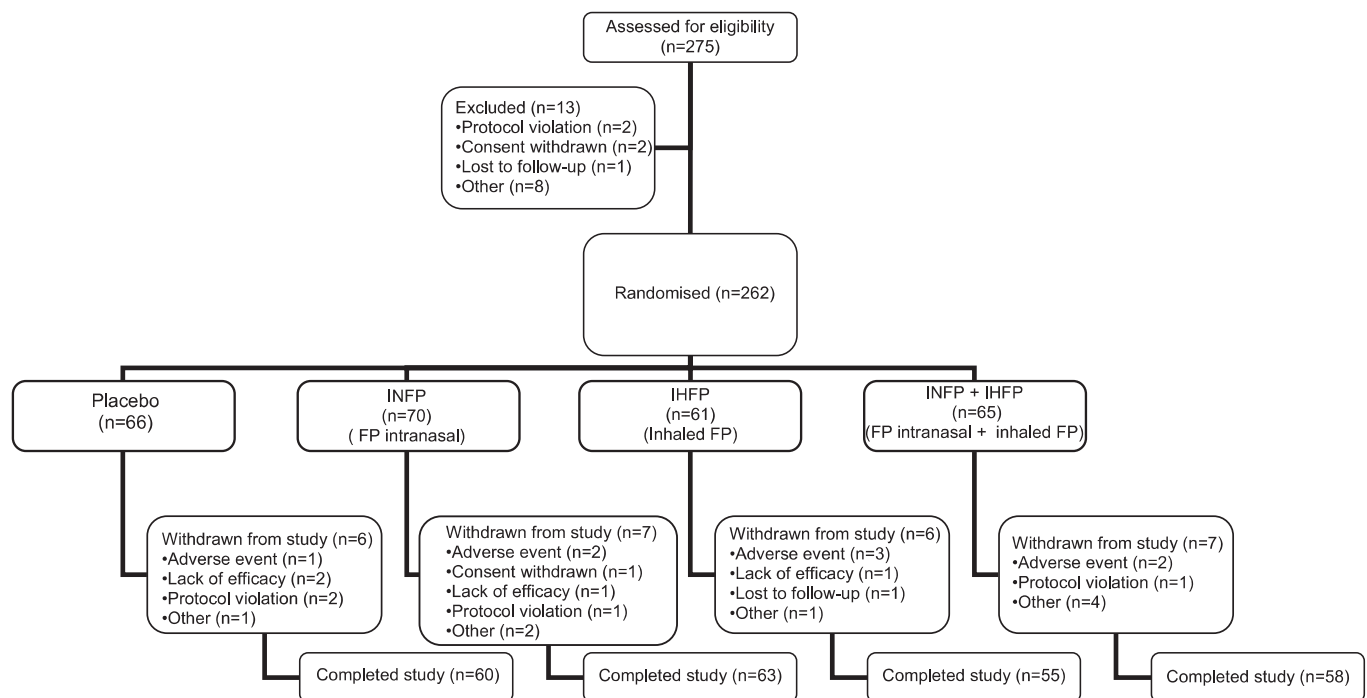


Figure 1. Disposition of the study patient population. Twenty-six patients did not complete the study: one withdrawal of consent, one lost to follow up, four lack of efficacy, four protocol violators, eight adverse events and eight for other reasons. INFP, fluticasone propionate nasal spray; IHFP, inhaled fluticasone propionate.

Table 1. Demographics and baseline lung function characteristics of study population

	Intranasal or inhaled placebo (n = 66)	INFP (n = 70)	IHFP (n = 61)	INFP + IHFP (n = 65)
Age (year), mean (SD)	31.8 (12.6)	35.5 (11.1)	33.1 (9.5)	34.9 (10.7)
Sex (M/F)	32/34	39/31	36/25	28/37
Lung function				
FEV ₁ (l), mean (SD)	3.7 (0.9)	3.6 (0.8)	3.7 (0.9)	3.6 (0.91)
PEF (l/min), mean (SD)	503 (103)	508 (132)	510 (103)	505 (125)

FEV₁, forced expiratory volume in 1 s; INFP, fluticasone propionate nasal spray; IHFP, inhaled fluticasone propionate; PEF, peak expiratory flow.

receiving IHFP (94.5%) and patients receiving no IHFP (93.9%) was statistically significant ($P < 0.05$).

The adjusted mean percentage of patients reporting no nasal blockage/congestion, no sneezing or no rhinorrhoea at the end of 6 weeks' treatment were significantly increased following treatment with INFP, compared with intranasal or inhaled placebo and IHFP alone (Fig. 2). The difference in percentage of days free of nasal blockage/congestion, sneezing or rhinorrhoea over the entire 6-weeks' treatment period between patients receiving INFP and patients not receiving INFP was significant ($P < 0.001$) for each symptom.

The mean percentage of days without use of intracocular levocabastine over the 6-week treatment period was also increased in all active treatment groups, compared with intranasal or inhaled placebo, and was significantly higher for INFP + IHFP, compared with no INFP treatment (data not shown; $P < 0.05$). Similarly, the mean percentage of days without oral acrivastine over the 6-week treatment period was increased in all active treatment groups, compared with intranasal or inhaled placebo, and was higher for INFP + IHFP, compared with no INFP treatment (data not shown; $P = 0.05$).

FEV₁

The FEV₁ over the entire 6-week treatment period was significantly higher ($P < 0.001$) in patients on IHFP, compared with patients not on IHFP.

Bronchial responsiveness to methacholine

Methacholine PD₂₀ was measured in 203 patients before and after 4 weeks' treatment. Before the pollen season, PD₂₀ was not measurable in 95 patients (i.e. PD₂₀ value was $>14.7 \mu\text{mol}$). Responsiveness to methacholine increased during the pollen season in patients treated with intranasal or inhaled placebo or INFP alone. No increase in methacholine responsiveness was seen in patients treated with IHFP ($P < 0.001$ compared to groups with no IHFP) (Fig. 3).

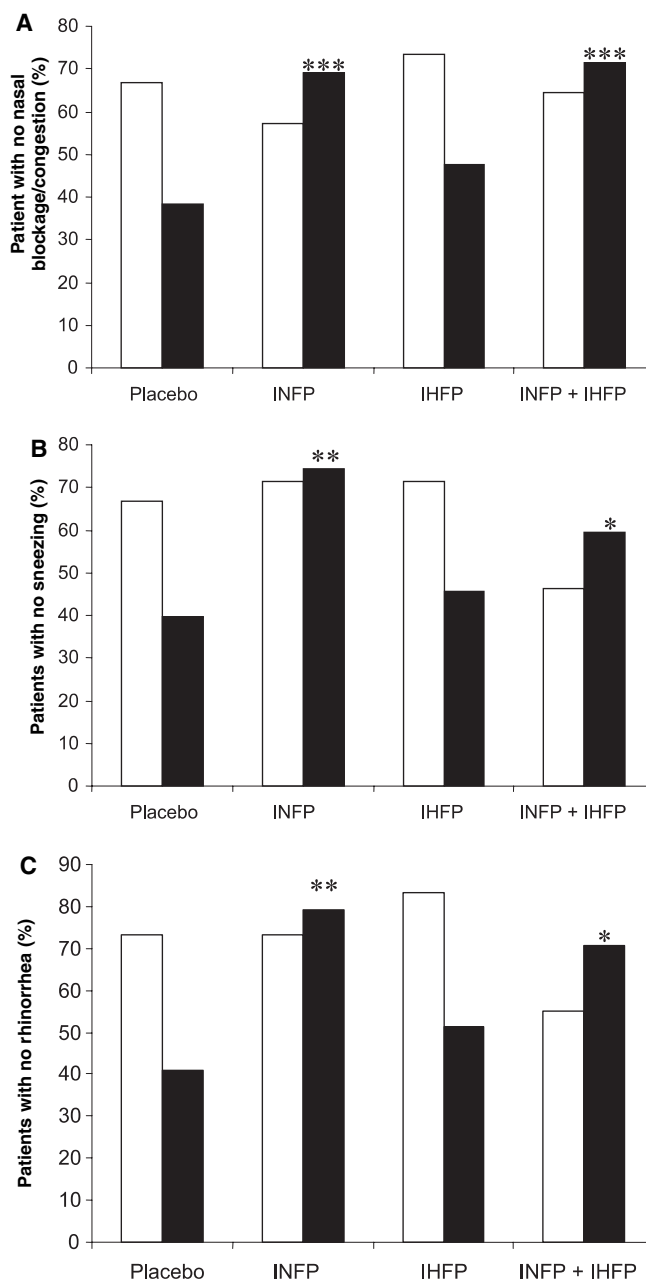


Figure 2. Percentage of patients reporting no (A) nasal blockage/congestion, (B) sneezing and (C) rhinorrhoea, at baseline and at week 6 (□, baseline; ■, weeks 1–6; * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ vs intranasal or inhaled placebo. INFP, fluticasone propionate nasal spray; IHFP, inhaled fluticasone propionate.

Induced sputum

Sputum induction was done in 64 patients at baseline and at the end of treatment. During the pollen season, the percentage of sputum eosinophils increased significantly in the intranasal or inhaled placebo and INFP groups alone, but was unchanged in the IHFP groups (Fig. 4).

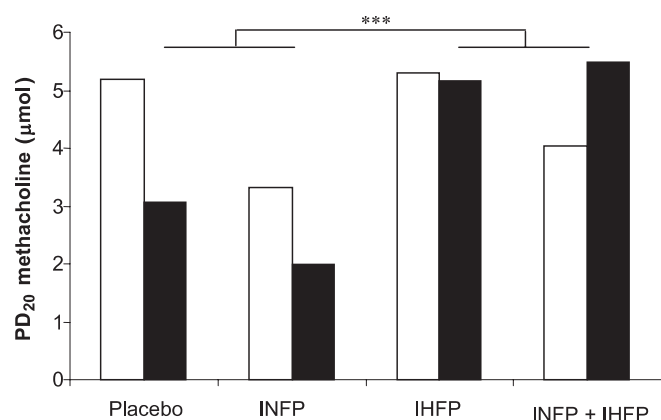


Figure 3. Geometric mean PD₂₀ methacholine measured at baseline (□) and after 4 weeks treatment (■) (***P* < 0.001 INFP ± INFP vs INFP or placebo). INFP, fluticasone propionate nasal spray; IHFP, inhaled fluticasone propionate.

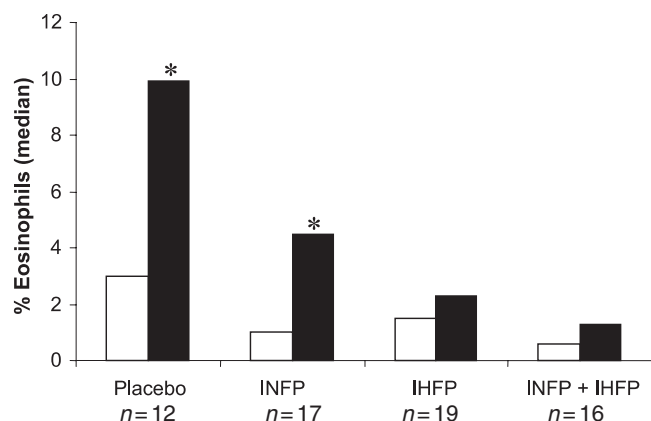


Figure 4. Percentage sputum eosinophils (□, baseline; ■, end of treatment; **P* < 0.05 for baseline vs end of treatment). INFP, fluticasone propionate nasal spray; IHFP, inhaled fluticasone propionate.

Macrophages, neutrophils and lymphocytes were neither altered during pollen season nor influenced by treatment (data not shown).

Adverse events

Reporting of adverse events during the study was similar across all the groups [19 subjects (29%) in the intranasal or inhaled placebo group, 19 (27%) in the INFP group, 18 (30%) in the IHFP group and 18 (28%) in the INFP + IHFP group]. The most common events were headache and asthma. Only one serious adverse event was reported – a neurological neoplasia of uncertain behaviour in one subject in the INFP + IHFP group, which was not considered to be drug-related by the reporting investigator. Nine subjects withdrew from the study

because of an adverse event, all but one of which were not considered to be serious.

Discussion

Pollen-induced rhinitis and asthma are frequently associated in the same patients. We used this association as a model to study the influence of local nasal or bronchial treatment with a topical corticosteroid on nasal and bronchial symptoms, bronchial responsiveness and inflammation. The results of our study show that nasal treatment with FP is effective in controlling nasal symptoms but does not influence asthmatic symptoms, bronchial responsiveness or inflammation. Treatment with IHFP is effective in controlling asthmatic symptoms, bronchial responsiveness and inflammation but has no influence on the nasal symptoms.

Our findings regarding the organ-selective effects of inhaled and nasal FP in patients with comorbid allergic asthma and rhinitis are in accordance with several smaller studies of comorbid allergic rhinitis and asthma, which have predominantly focused on the effects of intranasal steroid treatment in both the upper and lower airways. A study in adult patients with ragweed pollen-induced rhinitis and asthma has demonstrated that intranasal beclomethasone significantly improved rhinitis, but not asthma symptom scores or PEF (10). Similarly, a study in children with allergic asthma and chronic rhinitis demonstrated that although intranasal budesonide was effective in the treatment of nasal symptoms, it did not significantly alter wheeze, PEF, FEV₁ or FVC (11). A more recent study in a cohort of 72 children and young adults with immunoglobulin E (IgE)-mediated allergic rhinitis and mild asthma, also demonstrated that neither INFP nor beclomethasone dipropionate significantly altered bronchial responsiveness to methacholine in these patients, although nasal blockage, sneezing and rhinorrhoea were significantly decreased by both active treatments, when compared with placebo (16).

Our findings are, however, not in agreement with the findings of other small studies in patients with comorbid allergic rhinitis and asthma. Aubier et al. (17) investigated the effect of intranasal and intrabronchial beclomethasone dipropionate on carbachol-induced bronchial responsiveness in patients with persistent allergic rhinitis and found that intranasal, but not intrabronchial, beclomethasone dipropionate significantly decreased bronchial responsiveness in these patients. Other studies have demonstrated that intranasal budesonide (10), intranasal beclomethasone dipropionate (10, 18), and INFP (19) also protected significantly against methacholine-induced bronchial hyperresponsiveness in patients with seasonal or perennial allergic rhinitis and asthma, when compared with placebo. Interestingly, however, protection against methacholine challenge was afforded despite the lack of any significant protective effects on PEF or FEV₁ in these

studies. One study in seasonal allergic rhinitis, demonstrated that nasal beclomethasone dipropionate and flunisolide significantly decreased seasonal asthma symptoms scores from baseline, in addition to nasal symptom scores right across the pollen season, when compared with placebo or cromolyn treatment (20).

The frequent occurrence of asthma and allergic rhinitis in the same individual, the common triggers and similarities in pathogenesis and pathology have formed the basis for the 'united airways' concept (21–23), but comparatively few studies have investigated the effect of a single treatment modality on inflammatory indices in comorbid rhinitis and asthma (19, 24), and none have investigated the nasal effects of an inhaled corticosteroid.

Several mechanisms have been postulated to support the hypothetical effects of intranasal therapy in the lower airways. However, none of these have been substantiated. These include (i) direct and indirect anti-inflammatory effects of the drug in the lung, (ii) inhibition of mediator release or cellular translocation in the nose, (iii) prevention of systemic mediator absorption with distant effects in the lung, (iv) inhibition of nasobronchial neurogenic reflex and (v) effects related to the shift from nasal to oral breathing. It is possible that previously observed effects were a consequence of the use of topical corticosteroids with a higher degree of bioavailability, thus demonstrating a systemic impact of these drugs. The low systemic bioavailability of FP delivered via the intranasal route (12, 13) indicates that intranasal administered corticosteroids are unlikely to influence the lung directly or indirectly.

In conclusion, the effects of inhaled and INFP observed on symptoms and objective parameters investigated in our

study suggest that rhinitis and asthma are separate clinical manifestations and therefore require local treatment to be applied both in the nose and in the lower airways.

Conflict of interest

R. Dahl: Member of advisory board and/or lectures for: GSK, Boehringer-Ingelheim, Altana, Schering-Plough, MSD, ALK-Abello and UCB. Study grants from: AstraZeneca, GSK, ALK-Abello, Pfizer, Boehringer-Ingelheim, Novartis, Almirall and MSD. L. P. Nielsen: Lecturing at meeting sponsored by: AstraZeneca, GSK, Novartis, Schering-Plough and UCB. Consulted for: AstraZeneca and GSK. Participated in studies sponsored by: ALK-Abello, Almirall, AstraZeneca, Aventis, Boehringer-Ingelheim, Bristol Myers Squibb, Byk Gulden, GSK, Janssen-Cilag, MSD, Novartis, Pfizer, Pharmacia, Roche, Sanofi, Schering-Plough and UCB. A. Foresi: Has received travel support, research funding, fees for lecturing and consulting from: AstraZeneca, GSK and Schering-Plough. N. Tudoric: Payments for clinical research: GSK, Schering-Plough and MSD. Payments for lecturing: Bayer, GSK, Schering-Plough and MSD. D. H. Richards: Employee of GSK R&D. M. K. Williams: Employee of GSK R&D. R. Pauwels: Acted as consultant for GSK and other pharmaceutical companies. He has spoken at meetings sponsored by pharmaceutical companies and his department has received research grants from GSK and other pharmaceutical companies. J. C. Kips, P. van Cauwenberge, P. Howarth: No conflict of interest.

Acknowledgments

The authors thank the investigators and patients who participated in the study (FNM40001), GlaxoSmithKline R&D for funding the study and Dr J. L. Devalia (JD Scientific and Medical Communications, UK) for his assistance with the manuscript.

References

1. Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:S147–334.
2. Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997;**99**:S781–786.
3. Rowe-Jones JM. The link between the nose and the lung, perennial rhinitis and asthma – is it the same disease? *Allergy* 1997;**52**(Suppl. 36):20–28.
4. Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol* 1999;**104**:534–540.
5. Durham SR. Mechanisms of mucosal inflammation in the nose and lungs. *Clin Exp Allergy* 1998;**28**(Suppl. 2):11–16.
6. Togias A. Mechanisms of nose-lung interaction. *Allergy* 1999;**54**(Suppl. 57):94–105.
7. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23 year follow-up study of college students. *Allergy Proc* 1994;**15**:21–25.
8. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, Järvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med* 2000;**162**:920–924.
9. Simons FE. Is antihistamine (H₁-receptor antagonist) therapy useful in clinical asthma? *Clin Exp Allergy* 1999;**29**(Suppl. 3):98–104.
10. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;**90**:250–256.
11. Henriksen JM, Wenzel A. Effect of intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing and asthma. *Am Rev Respir Dis* 1984;**130**:1014–1018.
12. Szefer SJ. Pharmacokinetics of intranasal corticosteroids. *J Allergy Clin Immunol* 2001;**108**:S26–31.
13. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. *Br J Clin Pharmacol* 2001;**51**:103–105.
14. Sterk PJ, Fabbri LM, Quarnier Ph H, Cockcroft DW, O'Byrne PM, Anderson SD et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J Suppl* 1993;**16**:53–83.

15. Kips JC, Inman M, O'Connor B, Svensson K, Pauwels RA, O'Byrne PM. A long term study of the anti-inflammatory effect of low dose budesonide plus formoterol versus high dose budesonide in asthma. *Am J Respir Crit Care Med* 2000;**161**:996–1001.
16. Thio BJ, Slingerland GLM, Fredriks AM, Nagelkerke AF, Scheeren RA, Neijens HJ et al. Influence of intranasal steroids during the grass pollen season on bronchial responsiveness in children and young adults with asthma and hay fever. *Thorax* 2000;**55**:826–832.
17. Aubier M, Levy J, Clerici C, Neukirch F, Herman D. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. *Am Rev Respir Dis* 1992;**146**:122–126.
18. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993;**91**:97–101.
19. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms, and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996;**98**:274–282.
20. Welsh PW, Stricker WE, Chu C-P, Naessens JM, Reese ME, Reed CS et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;**62**:125–134.
21. Lipworth BJ, White PS. Allergic inflammation in the unified airway: start with the nose. *Thorax* 2000;**55**:878–881.
22. Passalacqua G, Canonica GW. Impact of rhinitis on airway inflammation: biological and therapeutic implications. *Respir Res* 2001;**2**:320–323.
23. Vinuya RZ. Upper airway disorders and asthma: a syndrome of airway inflammation. *Ann Allergy Asthma Immunol* 2002;**88**(Suppl. 1):8–15.
24. Pelucchi A, Chiapparino A, Mastropasqua B, Marazzini L, Hernandez A, Foresi A. Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens. *J Allergy Clin Immunol* 1995;**95**:515–523.

Appendix

Patients were enrolled by clinicians from nine European countries, as follows: Belgium – Prof. Johan Kips, Dr Jean Benoit Martinot, Dr Paul Reynders, Prof. Paul van Cauwenberge; Croatia – Dr Neven Tudoric; Denmark – Prof. Ronald Dahl, Dr John Heinig; Israel – Dr Arnon Goldberg; Italy – Prof. Caterina

Bucca, Dr Antonio Foresi, Dr S. S. A. Gianna Moscato, Prof. Pier Luigi Paggiaro, Prof. Andrea Siracusa; the Netherlands – Dr M. J. Mollers, Dr G. Nierop; Norway – Dr Knut Haavaag, Dr Arne Skag; Poland – Prof. Marek Kowalski; United Kingdom – Dr Peter Howarth.