Inflamm. Res. (2010) 59:391–398
DOI 10.1007/s00011-009-0117-4

Inflammation Research

ORIGINAL RESEARCH PAPER

The effects of bilastine compared with cetirizine, fexofenadine, and placebo on allergen-induced nasal and ocular symptoms in patients exposed to aeroallergen in the Vienna Challenge Chamber

Friedrich Horak · Petra Zieglmayer · René Zieglmayer · Patrick Lemell

Received: 6 April 2009 / Accepted: 3 October 2009 / Published online: 27 November 2009

Abstract
Objective and design This double-blind cross-over study compared the potential of bilastine, cetirizine, and fexofenadine to relieve the symptoms of allergic rhinitis.
Subjects and methods Seventy-five allergic volunteers were challenged with grass pollen in the Vienna Challenge Chamber (VCC) on two consecutive days of allergen provocation; 6 h on day 1 and 4 h day 2. Bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg, or placebo were taken orally 2 h after the start of provocation on day 1 only. Total nasal symptom scores, the global symptom scores, nasal secretions, and eye symptoms were assessed on both day 1 and day 2.
Results and conclusions Bilastine had a rapid onset of action, within 1 h, and a long duration of action, greater than 26 h. Cetirizine was similar. Fexofenadine was similar on day 1 but less effective on day 2, indicating a shorter duration of action. Bilastine, like cetirizine and fexofenadine, was safe and well tolerated in this study.

Keywords Bilastine · Cetirizine · Fexofenadine · Allergic rhinitis · Vienna Challenge Chamber

Responsible Editor: C. Kasserra.

F. Horak (✉)
ENT Department, Medical University Vienna,
Waehringer Guertel 18, 1090 Vienna, Austria
e-mail: friedrich.horak@vienna.at

P. Zieglmayer · R. Zieglmayer · P. Lemell
VCC Department, Allergy Centre Vienna West,
Huetteldorferstrasse 44, 1150 Vienna, Austria

Introduction

Seasonal allergic rhinitis (SAR) is a disease that has increased dramatically in prevalence over the last century. The International Study of Asthma and Allergies in Childhood (ISAAC) epidemiological research program has revealed that in many developed countries the prevalence of SAR in adolescents is 15–20% with some countries reporting up to 45% prevalence [1]. Using a conservative estimate, allergic rhinitis now affects the lives of over 500 million people worldwide [2]. Furthermore, it is now recognized that allergic rhinitis comprises more than the classic symptoms of sneezing, rhinorrhoea, and nasal obstruction; it is associated with a significant impairment of the ability of patients to function in day-to-day life because of declined cognitive processing, psychomotor speed, verbal learning, and memory during allergy season [3]. Not only does this affect a patient's quality of life, but untreated allergic rhinitis also carries a significant financial burden for society (costs of medication, physician visits, hospitalizations, and loss of productivity at work), which, for persistent allergic rhinitis in France in 2002, was estimated at 355.06 Euro per patient per month [4]. Thus, effective treatment of allergic rhinitis is imperative.

Antihistamines are effective medications that have been used for decades in the management of allergic rhinitis. The properties of the chosen drug should include good clinical efficacy in relieving sneezing, rhinorrhoea, and nasal itching; anti-inflammatory properties to reduce nasal obstruction [5]; a rapid onset of action; and a long duration of effect. In addition, as recommended by the consensus document of the antihistamine impairment roundtable in 2003, the drug should not cause sedation or mental impairment even when administered at higher than recommended doses [6].

In this study, the ability of bilastine to relieve the symptoms of allergic rhinitis has been compared with that of cetirizine and fexofenadine. Both cetirizine and fexofenadine are well established in the treatment of allergic rhinitis [7, 8] while bilastine is a newly developed drug. Preclinical studies have shown that bilastine is a potent H_1-antihistamine with a high selectivity for H_1-receptors and poor or no affinity for other receptors, including serotonin, bradykinin, leukotriene-D_4, muscarinic M_3-receptors, α_1-adrenoceptors, β_2-adrenoceptors, and H_2- and H_3-histamine receptors [9]. By use of the Shultz–Dale reaction, bilastine has also been shown to have anti-inflammatory properties [9]. In clinical studies, bilastine has been shown to have a rapid onset of action and a long duration of effect [10, 11]. Furthermore, bilastine has been shown to be free of cardiotoxicity [12] and sedative effects within the CNS and not to enhance the effects of lorazepam [13], the latter property supported by the observation that bilastine is a substrate for P-glycoprotein, an organic anion transporting protein (OATP) that prevents its uptake across the blood–brain barrier into the brain [14].

In this study, the potential of bilastine 20 mg, cetirizine 10 mg, and fexofenadine 120 mg to relieve the symptoms of allergic rhinitis has been compared in the Vienna Challenge Chamber (VCC), a standardized method of challenging up to 20 subjects at a time with controlled levels of allergens for prolonged periods [15–17].

Protocols and methods

This was a single center, double-blind, randomized, placebo-controlled, balanced four-treatment, four-period crossover phase II study performed outside of the pollen season in individuals with asymptomatic SAR. In each study period, over 2 consecutive days, the subjects were exposed to a controlled concentration of grass pollen in the VCC as described elsewhere [16, 18]. The study was performed in accordance with the Declaration of Helsinki (as amended in 1964) and in compliance with the ICH E6 Note for Guidance on Good Clinical Practices (CPMP/ICH/135/95). It was approved by the appropriate independent ethics committee and regulatory authorities before the start of the study. Informed consent was obtained from each subject.

Study population

A total of 75 healthy individuals between 18 and 55 years of age [mean 28.3 ± 6.0 (SD) years; 43 F and 32 M] with a documented allergy to grass pollens (positive history, skin prick test, and spec. IgE-RAST ≥ class 2) but who were free from clinically significant illness or disease as determined by their medical history, physical examination, laboratory studies, and other tests, were enrolled in the study. Women of childbearing potential were eligible if they were not sexually active or if they were following a medically accepted contraceptive method. Subjects were excluded from the study if they used the following medications (number of days before start of study): systemic or topical corticosteroids (30); ketotifen, nedocromil, or cromoglycate (14); systemic or topical antihistamines (10); systemic theophylline (7); systemic or topical decongestants (3); or any sympathomimetics, including nasal and eye drops (1). Subjects with structural nasal abnormalities, nasal polyposis, a history of frequent nosebleeds, recent nasal surgery, or recent (within 3 weeks) or ongoing upper respiratory tract infection were excluded from the study.

Evaluation of total nasal symptom score

Total nasal symptom score (TNSS) was composed of the sum of four individual symptom scores (sneezing, rhinorrhoea, nasal obstruction, and nasal itching), each assessed every 15 min on a 4-point scale: 0 = none (no signs/symptoms), 1 = mild (signs/symptoms clearly present, minimal awareness, easily tolerated), 2 = moderate (definite awareness of signs/symptoms, bothersome but tolerable), 3 = severe (signs/symptoms hard to tolerate, interfered with planned activities during allergen exposure). The maximum score for TNSS was 12 for each recorded time point.

Screening period

During the screening period, between 7 and 28 days before the first treatment period, subjects provided informed consent, inclusion and exclusion criteria were checked, and demographic and clinical baseline data were assessed. The screening included exposure to allergen for 3 h (1,500 grass pollen grains/m^3) in the VCC to check that subjects had a positive response to allergen defined as a TNSS of at least 6 and two symptoms moderate or severe in two consecutive subjective scoring assessments during the first 2 h of the session. After 2 h, a single dose of placebo was administered. Placebo responders were discontinued from the study. These were defined as subjects who had reduced symptoms (>2 symptom scoring points from the qualification score) at the last scoring in the following hour of the session. Subjects who successfully completed this phase were randomized and entered the treatment phase.

Treatment period

Each treatment period comprised 2 consecutive days that included 6 h of allergen provocation (1,500 grass pollen grains/m^3) on day 1 followed by a further 4 h of

provocation with the same concentration of allergen on day 2 [16, 18].

All patients were symptom free before each treatment period. During each treatment period, subjects took one single dose of the respective drug (tablets of bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg, or placebo encased in an opaque oral capsule to ensure blinding [17]), 2 h after the start of the challenge on day 1. The sequence of medications applied during the treatment periods followed a randomized order according to a balanced cross-over design. Subjects left the unit after the 6 h of measurements on day 1 were completed and returned the following morning for the day 2 assessments during the 4 h allergen provocation period 22–26 h after drug or placebo administration. No further medication was administered on this day. There was a washout phase of at least 7 days between the treatment periods.

No rescue therapy was allowed for the alleviation of allergic rhinitis symptoms during the treatment period. However, during the time spent in the VCC and thereafter, the use of a local β_2-sympathomimetic inhaler for immediate relief of asthmatic symptoms was allowed, but not used, in this study. The following treatments were prohibited between the first and last visits: corticosteroids (systemic and topical), ketotifen, nedocromil, cromoglycate, theophylline (systemic), all other antihistamines, decongestants (systemic, local), all sympathomimetics (including nose and eye drops), and ongoing desensitization.

Study objectives

Primary objective

The primary objective of this study was to compare the effects of a single dose of bilastine 20 mg (74 individuals) with those of cetirizine 10 mg (68 individuals), fexofenadine 120 mg (70 individuals), and placebo (70 individuals) on the TNSS in subjects with SAR exposed to an allergen for 6 h in the VCC. A single dose of the trial drug was administered 2 h after the start of the allergen challenge on day 1.

Secondary objectives

The speed of onset of action (defined as the first assessment of TNSS after drug application with $P < 0.05$ vs. placebo) and the duration of action of each active medication (assessed from results during the 4 h exposure to allergen on day 2, 22–26 after drug administration) were assessed for each active medication.

Global symptom score was assessed as the composite score for nasal obstruction, rhinorrhoea, itchy nose, sneezing, watery eyes, itchy eyes and red eyes, cough, itchy throat, itchy ears. Further secondary objectives included a study of the individual components that comprise the TNSS: rhinorrhoea, itching nose, sneezing and nasal obstruction (anterior rhinomanometry), and the subjective scoring of eye symptoms, including watery eyes, itchy eyes, and red eyes.

Nasal secretion was estimated by weighing tissues before and after use. The subjects used tissues as necessary and at least every 30 min to collect nasal secretions for weighing during allergen exposure. The weight of the secretions was determined by weighing disposable paper handkerchiefs before and after use. Every 30 min a pre-packed and weighed set of handkerchiefs was handed out to each subject. The paper handkerchiefs were collected in pre-weighed plastic bags, which were kept closed. After weighing the pre-packed and used handkerchiefs, the difference in weights was recorded to 0.01 g.

Nasal air flow, the sum of that for the left and right nostrils, was measured prior to dosing and every 30 min until the end of the challenge session by active anterior rhinomanometry at a pressure of 150 Pascal by means of a rhinomanometer [16]. Nasal air flow was expressed as the volume of air/second (cm^3/s).

Safety and tolerability

The safety and tolerability of the study drugs was assessed throughout the study and during a follow-up of between 7 to 14 days after the last dose administered. At this visit safety evaluations were performed, including hematology, clinical chemistry, urinalysis, recording of vital signs (blood pressure, heart rate) and electrocardiogram and FEV_1 in case of occurrence of asthma symptoms. All subjects were asked about their state of health, adverse events, and about the use of any concomitant medication.

Statistical methods

Primary and secondary efficacy variables were analyzed using the PROC MIXED procedure of SAS. The model had baseline as covariate, treatment and period as fixed effects, and a random intercept for each subject. No carry-over effect was anticipated due to the presence of a sufficient washout period time between the treatment periods. The sample size of 75 patients was chosen from experience with similar studies [16–19]. A probability value of $P = 0.05$ was taken as the minimum level of statistical significance.

Results

Out of a total of 75 individuals randomized, 67 completed the study. Seven patients discontinued the study for personal reasons. One patient was discontinued by the investigator because of concurrent sinusitis. Before drug

administration in each of the treatment periods, subjects had allergen-induced symptom severities similar to those observed during the screening session.

Primary objective: total nasal symptom score

The effects of bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg, and placebo administered 2 h after the start of the allergen challenge on the TNSS in subjects with SAR exposed to allergen for 6 h on day 1 in the VCC are shown in Fig. 1a. For day 1, the sum of the TNSS score for bilastine 20 mg for the 4 h after drug dosing was 111.2 ± 4.3 (mean ± SEM), which represents a reduction of 16.7% from the placebo value of 133.6 ± 4.7 ($P < 0.001$). The corresponding score for cetirizine 10 mg was 107.5 ± 4.6 (a 19.5% reduction from placebo, $P < 0.001$) and that for fexofenadine was 113.6 ± 4.6 (a 15.0% reduction from placebo, $P < 0.001$). There were no statistically significant differences in the effects of the three antihistamines (Table 1).

Secondary objectives

Onset of action

The speed of onset of action (defined as the first assessment of TNSS after drug application with $P < 0.05$ vs. placebo) was 1 h for all three drugs. There were no statistically significant differences between the effects of the three antihistamines (Fig. 1a).

Duration of action

The duration of action of each active medication was assessed from the sum of the scores at the individual time points during the 4 h exposure to allergen on day 2 (22–26 h after drug administration) (Fig. 1b). The sum of the TNSS score for bilastine 20 mg for this period was 106.2 ± 4.2 (mean ± SEM), a reduction of 21.8% from the placebo value of 135.96 ± 4.4 ($P < 0.001$) indicating that drug activity persists for at least 26 h. The corresponding score for cetirizine 10 mg was 99.4 ± 5.0 (a 27.0% reduction from placebo, $P < 0.001$) and that for fexofenadine was 119.3 ± 4.4 (a 12.2% reduction from placebo, $P < 0.001$). Comparisons of the effects of the three antihistamines revealed that, although there was no statistical difference between the activities of bilastine and cetirizine, both bilastine ($P = 0.0012$) and cetirizine ($P < 0.001$) were significantly more active than fexofenadine between 22 and 26 h after dosing suggesting that they have a longer duration of action.

Global symptom score

The effects of bilastine, cetirizine, fexofenadine, and placebo for the period between 0 and 4 h after drug

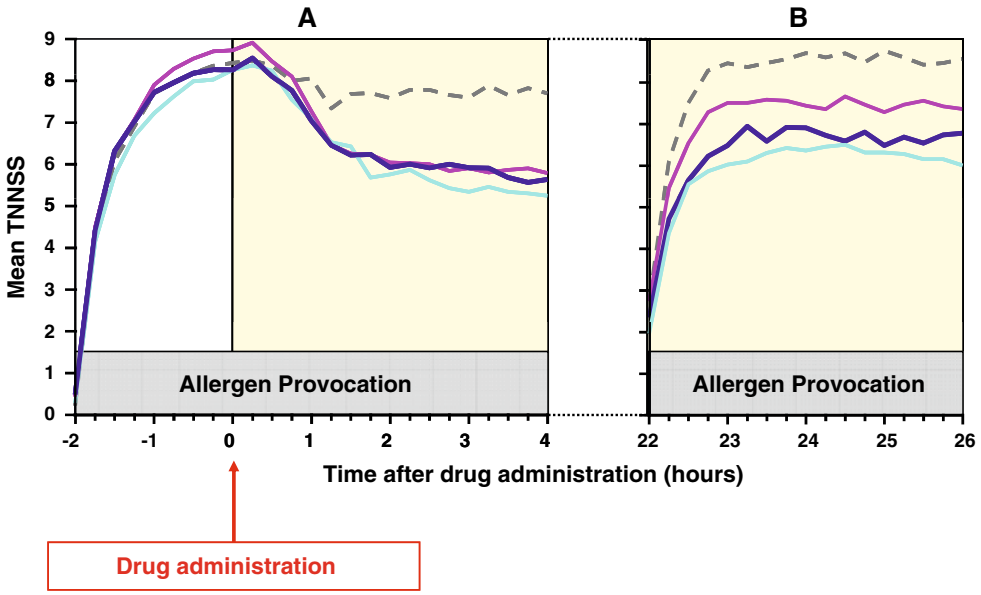

Fig. 1 The time course of the effects of bilastine 20 mg (*dark blue line*, $n = 74$), cetirizine 10 mg (*light blue line*, $n = 68$), fexofenadine 120 mg (*magenta line*, $n = 70$), and placebo (*grey broken line*, $n = 70$) against the allergen-induced increase in total nasal symptom score (TNSS) assessed every 15 min in the Vienna Challenge Chamber. Subjects were exposed to 6 h of allergen provocation on day 1 (**a**) followed by a further 4 h of provocation with the same concentration of allergen on day 2 (**b**). Drugs were administered orally only once, 2 h after the commencement of allergen exposure on day 1 (time 0 on the graph). Day 2 assessed the effects of the drugs from 22 to 26 h after administration (color figure online)

Table 1 Global symptom score on day 1, sum of all time points between 0 and 4 h after drug intake

	Placebo	Bilastine	Cetirizine	Fexofenadine
Mean ± SEM	212.5 ± 10.2	172.0 ± 8.1	164.8 ± 8.0	176.5 ± 8.2
No. of subjects	70	74	68	70
Significance vs. placebo	–	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Significance vs. bilastine	–	–	$P = 0.727$	$P = 0.168$
Significance vs. cetirizine	–	–	–	$P = 0.101$

administration on day 1 are seen in Table 1. During this period, the global symptom score for bilastine was reduced by 19.1% from placebo ($P < 0.0001$). The corresponding reduction from placebo for cetirizine was 22.4% ($P < 0.0001$) and that for fexofenadine 16.9% ($P < 0.0001$). There were no statistically significant differences in the effects of the three antihistamines.

The effects of bilastine, cetirizine, fexofenadine, and placebo for the period between 22 and 26 h after drug administration are seen in Table 2. All the active compounds were significantly different from placebo. During this period, the global symptom score for bilastine was reduced by 24.3% from placebo ($P < 0.0001$). The corresponding reduction from placebo for cetirizine was 31.2% ($P < 0.0001$) and that for fexofenadine 11.5% ($P < 0.0023$). There was no statistical difference between the activities of bilastine and cetirizine ($P = 0.355$), but both bilastine ($P = 0.0004$) and cetirizine ($P < 0.0001$) were significantly more active than fexofenadine between 22 and 26 h after dosing, suggesting them to have a longer duration of action.

Individual nasal symptoms

In exploring the individual components that comprise the TNSS, a consistent rapid onset of action was obtained against three of the four symptoms (i.e., rhinorrhoea, itching nose, and sneezing), all drugs being active within 1 h of administration. Of these, the effect of bilastine was most pronounced against sneezing (29% reduction from placebo at 1 h, $P < 0.0001$). The fourth component, nasal obstruction, was less well reduced, with the first significant inhibition of 7% ($P = 0.019$) being recorded 2 h 15 min after bilastine administration. A similar delayed onset of action was seen with cetirizine and fexofenadine for nasal obstruction.

Comparisons of the effects of the three antihistamines at 26 h showed that all were still significantly effective against rhinorrhoea, itching nose, and sneezing ($P < 0.05$), but not nasal obstruction. As with the TNSS, both bilastine and cetirizine were significantly ($P < 0.05$) more active than fexofenadine against rhinorrhoea and sneezing at this time point suggesting them to have a longer duration of action.

Eye symptoms

The subjective findings in terms of eye symptoms (watery eyes, itchy eyes, and red eyes) supported the results of nasal symptoms in that they were significantly ($P < 0.03$) reduced by bilastine by 1 h after drug intake; the mean ± SEM for the composite eye scores for placebo and bilastine were 0.95 ± 0.11 and 0.74 ± 0.09. There were no statistically significant differences in the effects of bilastine, cetirizine, and fexofenadine at this time.

Bilastine also had a long duration of action against eye symptoms, still being significantly ($P < 0.03$) effective 26 h after administration. The mean ± SEM for the composite eye scores for placebo and bilastine at this time were 1.05 ± 0.11 and 0.80 ± 0.11. While the effects of cetirizine were also significantly different from placebo at this time ($P < 0.001$), those of fexofenadine were not ($P = 0.541$), indicating this drug to have a shorter duration of action.

Nasal secretion

The effects of bilastine, cetirizine, fexofenadine, and placebo administered 2 h after the start of the allergen challenge on nasal secretion are shown in Fig. 2. For day 1,

Table 2 Global symptom score on day 2, sum of all time points between 22 and 26 h after drug intake

	Placebo	Bilastine	Cetirizine	Fexofenadine
Mean ± SEM	218.1 ± 10.0	165.4 ± 8.7	150.4 ± 8.7	193.2 ± 9.9
No. of subjects	70	74	68	70
Significance vs. placebo	–	$P < 0.0001$	$P < 0.0001$	$P < 0.0023$
Significance vs. bilastine	–	–	$P = 0.355$	$P = 0.0004$
Significance vs. cetirizine	–	–	–	$P < 0.0001$

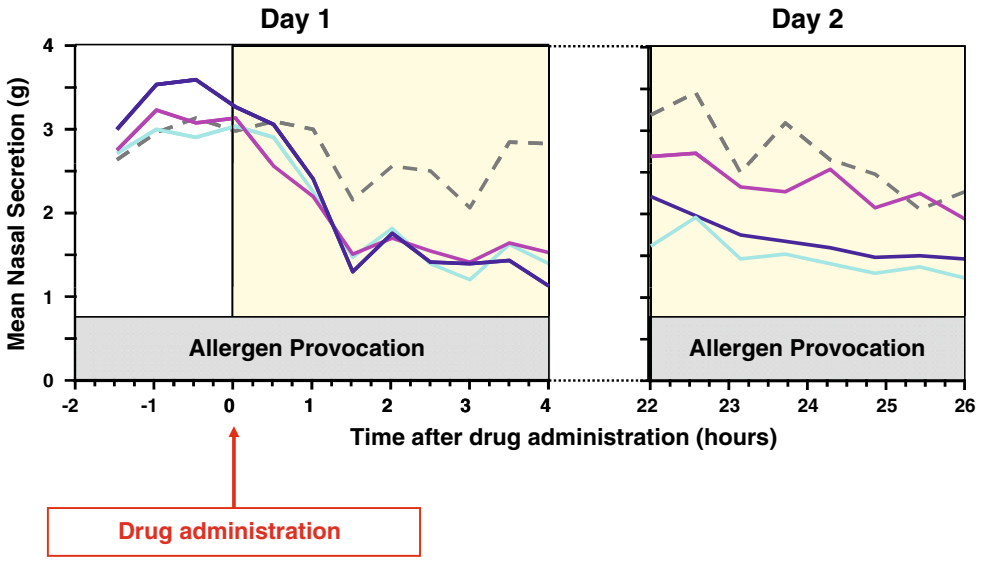

Fig. 2 The time course of the effects of bilastine 20 mg (*dark blue line*, $n = 74$), cetirizine 10 mg (*light blue line*, $n = 68$), fexofenadine 120 mg (*magenta line*, $n = 70$), and placebo (*grey broken line*, $n = 70$) against the allergen-induced increase in nasal secretion in the Vienna Challenge Chamber (VCC). Subjects were exposed to 6 h of allergen provocation on day 1 (**a**) followed by a further 4 h of provocation with the same concentration of allergen on day 2 (**b**). Drugs were administered orally only once, 2 h after the commencement of allergen exposure on day 1 (time 0 on the graph). Day 2 assessed the effects of the drugs from 22 to 26 h after administration (color figure online)

the weight of nasal secretion for bilastine for the 4 h after drug dosing was 17.2 ± 1.9 g (mean ± SEM), a reduction of 28.7% from the placebo value of 24.1 ± 2.5 g ($P < 0.0001$). The corresponding amount of nasal secretion for cetirizine was 17.11 ± 1.8 g (a 29.0% reduction from placebo, $P < 0.001$) and that for fexofenadine was 17.3 ± 1.9 g (a 28.4% reduction from placebo, $P < 0.0001$). There were no statistically significant differences in the effects of the three antihistamines.

During the allergen challenge on day 2 (22–26 h after drug administration), the mean weight of nasal secretion in the bilastine-treated group was 13.6 ± 1.6 g (mean ± SEM), a reduction of 37.1% from the placebo value of 21.6 ± 1.6 g ($P < 0.0001$) indicating that drug activity persists for at least 26 h. The corresponding amount of secretion for cetirizine was 11.8 ± 5.0 g (a 45.3% reduction from placebo, $P < 0.0001$) and that for fexofenadine was 18.7 ± 1.7 g (a 13.5% reduction from placebo, $P < 0.044$). As with TNSS, there was no statistical difference in the activities of bilastine and cetirizine but both bilastine ($P < 0.0001$) and cetirizine ($P < 0.0001$) were significantly more active than fexofenadine between 22 and 26 h after dosing, suggesting that they have a longer duration of action.

Nasal airflow

None of the three antihistamines tested significantly affected the allergen-induced reduction of nasal airflow on either day 1 or day 2.

Safety and tolerability

No serious adverse events occurred in this study. Six subjects experienced at least one adverse event with a total of eight adverse events being reported. Two adverse events were rated as possibly related to bilastine (two subjects with epistaxis, each on day 2), two adverse events were documented as possibly related to cetirizine (one subject with tachycardia and vertigo on day 1). The other adverse events were regarded as not related to treatment or the challenge procedure: decreased potassium (before visit 1), common cold (before visit 1), common cold between visit 2 and visit 3.

One subject developed sinusitis after visit 4 and was discontinued by the investigator.

All adverse events were resolved, and—with the exception of the discontinuation of the subject with sinusitis—no special action was necessary.

Discussion

During the 4 h of exposure of asymptomatic SAR subjects to grass pollen following medication, bilastine 20 mg provided statistically significant protection against the development of nasal symptoms, as assessed with TNSS, when compared to placebo. Bilastine began to be significantly effective 1 h after administration. That it was also significantly effective between 22 and 26 h after drug

intake indicates that its duration of activity is at least 26 h after administration. Similar results were obtained with cetirizine 10 mg. Although the effects of bilastine and fexofenadine 120 mg were similar during the first 4 h after administration, bilastine and cetirizine were significantly more effective than fexofenadine between 22 and 26 h after drug intake suggesting bilastine to have a longer duration of action. This result is consistent with published data concerning the duration of action of fexofenadine [16, 17]. All medications used were safe and well tolerated in this study population.

When exploring the individual nasal symptoms that comprise the TNSS, rhinorrhoea, itching nose, and sneezing were particularly well inhibited. This finding confirms other results in the VCC [16, 17, 19] and in clinical trials of allergic rhinitis [2, 20] with most H_1-antihistamines with the exception of desloratadine [21–23].

Conversely, all three antihistamines tested were weakly effective against nasal obstruction evaluated subjectively by patients and did not significantly reduce nasal airflow measured objectively using rhinomanometry. Again, this finding confirms previous results in the VCC [17, 19]. Studies in clinical allergic rhinitis have shown that there is a clear relationship between Th2-related nasal inflammation and reduced nasal airflow in patients with allergic rhinitis [24] that is slow to respond to therapy [25, 26]. As the transcription factor NF-κB, which is pivotally involved in the development of allergic inflammation, may be stimulated via the histamine H_1-receptor [5], then allergic inflammation will be reduced by all H_1-antihistamines, the degree of effect being dependent on their potency and the duration of treatment period.

One consistent feature of this study was that bilastine had a longer duration of action than fexofenadine. This was seen in the results from TNSS, global symptom score, nasal secretion, and eye symptoms 22 to 26 h after drug administration. The reason for this difference is likely to lie in the differential susceptibility of the drugs to efflux and uptake transporters such as P-glycoprotein, multidrug resistance-associated proteins (MRPs), or organic anion transporting polypeptides (OATPs), which play a critical role in the active transport of many drugs across biological membranes [27]. Perhaps the most researched of these is P-glycoprotein, which is critically involved in reducing the passage of bilastine and fexofenadine across the blood–brain barrier, thereby minimising their CNS effects [14, 28]. However, not only are these transporters of protective significance at the blood–brain barrier, but they are also expressed at physiological sites of drug absorption and elimination, thus leading to diminished absorption and/or increased transporter-facilitated excretion. With fexofenadine, for example, it is now becoming clear that other transporters in addition to P-glycoprotein are also involved in determining the pharmacokinetic profiles of these drugs [28–30]. It is not yet known if bilastine, like fexofenadine, is also a substrate for these other multidrug resistant-associated protein transporters, but its prolonged duration of action suggests that it is not.

In conclusion, bilastine 20 mg has been shown to be an effective H_1-antihistamine in the relief of nasal and ocular symptoms of seasonal allergic rhinoconjunctivitis induced by exposure of allergic individuals to grass pollen in the VCC. Bilastine had a rapid onset of action, within 1 h of administration, and a long duration of action, greater than 26 h. A similar profile was seen with cetirizine 10 mg. Fexofenadine 120 mg also had a similar profile during the first 4 h after dosing. However, the observation that bilastine was significantly more effective than fexofenadine in reducing the TNSS, the global symptom score, nasal secretions, and eye symptoms 22 to 26 h after drug administration indicates that bilastine had a longer duration of action than fexofenadine. Bilastine, like cetirizine and fexofenadine, was safe and well tolerated in this study population.

Acknowledgments The authors thank FAES FARMA, Bilbao, Spain, for financial assistance.

References

1. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733–43.
2. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update [in collaboration with the World Health Organization, GA(2)LEN and AllerGen]. Allergy. 2008;63(Suppl 86):8–160.
3. Blaiss MS. Important aspects in management of allergic rhinitis: compliance, cost, and quality of life. Allergy Asthma Proc. 2003;24:231–8.
4. Bousquet J, Demarteau N, Mullol J, van den Akker-van Marle ME, Van Ganse E, Bachert C. Costs associated with persistent allergic rhinitis are reduced by levocetirizine. Allergy. 2005;60:788–94.
5. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy. 2002;32:489–98.
6. Casale TB, Blaiss MS, Gelfand E, Gilmore T, Harvey PD, Hindmarch I, et al. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. J Allergy Clin Immunol. 2003;111:S835–42.
7. Meltzer EO, Grant JA. Impact of cetirizine on the burden of allergic rhinitis. Ann Allergy Asthma Immunol. 1999;83(5):455–63.
8. Markham A, Wagstaff AJ. Fexofenadine. Drugs. 1998; 55:269–74.
9. Corcostegui R, Labeaga L, Innerarity A, Berisa A, Orjales A. Preclinical pharmacology of bilastine, a new selective histamine H1 receptor antagonist: receptor selectivity and in vitro antihistaminic activity. Drugs R D. 2005;6:371–84.

10. Sologuren A, Valiente R. Relationship of dose to inhibition of wheal and flare for 5 doses bilastine and 10 mg cetirizine. In: Proceedings of the 36th ACCP Annual Meeting, San Francisco, CA, 9–11 September; 2007.
11. Audicana MT. A double blind, randomized, dose ranging trial in four parallel groups of 10, 20 and 30 mg bilastine once daily vs placebo in the symptomatic treatment of chronic idiopatic urticaria. In: Proceedings of SEIAC, Santander (Spain); 2007.
12. Alison M, Benoit T, Sologuren A. Lack of significant effect of bilastine on ventricular repolarization. A throrough QT/QTc study. In: Proceedings of the EAACI Congress, Barcelona (Spain), 7–11 June; 2008.
13. Garcia-Gea C, Martinez-Colomer J, Antonijoan RM, Valiente R, Barbanoj MJ. Comparison of peripheral and central effects of single and repeated oral dose administrations of bilastine, a new H1 antihistamine: a dose-range study in healthy volunteers with hydroxyzine and placebo as control treatments. J Clin Psychopharmacol. 2008;28:675–85.
14. Gonzalo A, Lucero ML, Orjales A. Early identification of the processes involved in bilastine bioavailability in rats. In: Proceedings of 10th European Regional ISSX Meeting, Vienna, Austria, 18–21 May; 2008.
15. Horak F, Jäger S. Wiener Provokations-Kammer (Vienna Challenge Chamber): eine neue Methode des Allergenexpositionstests. Wiener klin Wochenschr. 1987;99:509–10.
16. Horak F, Stübner UP, Zieglmayer R, Kavina A, De Vos C, Burtin B, et al. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. Int Arch Allergy Immunol. 2001;125:73–9.
17. Horak F, Zieglmayer PU, Zieglmayer R, Kavina A, Lemell P. Levocetirizine has a longer duration of action on improving total nasal symptoms score than fexofenadine after single administration. Br J Clin Pharmacol. 2005;60:24–31.
18. Stuebner P, Zieglmayer R, Horak F. A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit—the Vienna Challenge Chamber (VCC). Curr Med Res Opin. 2004;20:891–902.
19. Stuebner P, Horak F, Zieglmayer R, Arnaiz E, Leuratti C, Perez I, et al. Effects of rupatadine vs placebo on allergen-induced symptoms in patients exposed to aeroallergens in the Vienna Challenge Chamber. Ann Allergy Asthma Immunol. 2006;96:37–44.
20. Canonica GW, Bousquet J, Van HG, Bachert C, Durham SR, Klimek L, et al. Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis. Respir Med. 2006;100:1706–15.
21. Horak F, Stübner UP, Zieglmayer R, Harris AG. Effect of desloratadine versus placebo on nasal airflow and subjective measures of nasal obstruction in subjects with grass pollen-induced allergic rhinitis in an allergen-exposure unit. J Allergy Clin Immunol. 2002;109:956–61.
22. Horak F, Stübner UP. Decongestant activity of desloratadine in controlled-allergen-exposure trials. Clin Drug Invest. 2002; 22(Suppl 2):13–20.
23. Horak F, Stübner UP, Zieglmeyer R, Harris AG. Comparison of the effects of desloratadine 5-mg daily and placebo on nasal airflow and seasonal allergic rhinitis symptoms induced by grass pollen exposure. Allergy. 2003;58:481–5.
24. Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Correlation of nasal inflammation and nasal airflow with forced expiratory volume in 1 second in patients with perennial allergic rhinitis and asthma. Ann Allergy Asthma Immunol. 2004;93:575–80.
25. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. Clin Exp Allergy. 2004;34:958–64.
26. Ciprandi G, Cirillo I, Vizzaccaro A, Civardi E, Barberi S, Allen M, et al. Desloratadine and levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with perennial allergic rhinitis: a pilot study. Int Immunopharmacol. 2005; 5(13–14):1800–8.
27. Oswald S, Grube M, Siegmund W, Kroemer HK. Transporter-mediated uptake into cellular compartments. Xenobiotica. 2007;37(10–11):1171–95.
28. Tahara H, Kusuhara H, Fuse E, Sugiyama Y. P-glycoprotein plays a major role in the efflux of fexofenadine in the small intestine and blood-brain barrier, but only a limited role in its biliary excretion. Drug Metab Dispos. 2005;33:963–8.
29. Matsushima S, Maeda K, Hayashi H, Debori Y, Schinkel AH, Schuetz JD, et al. Involvement of multiple efflux transporters in hepatic disposition of fexofenadine. Mol Pharmacol. 2008;73:1474–83.
30. Tian X, Zamek-Gliszczynski MJ, Li J, Bridges AS, Nezasa K, Patel NJ, et al. Multidrug resistance-associated protein 2 is primarily responsible for the biliary excretion of fexofenadine in mice. Drug Metab Dispos. 2008;36:61–4.