ORIGINAL ARTICLE

Fluticasone furoate versus placebo in symptoms of grass-pollen allergic rhinitis induced by exposure in the Vienna Challenge Chamber

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ABSTRACT

Objective: The Vienna Challenge Chamber (VCC) offers a controlled and controllable paradigm in which to reproducibly evaluate the efficacy of anti-allergic treatment. The aim of this study was to assess the efficacy of the novel intranasal corticosteroid fluticasone furoate (FF) in the VCC.

Methods: The single-centre, randomised, double-blind, placebo-controlled, two-period crossover study was conducted in 59 adult males with grass pollen allergic rhinitis (AR). Patients received either Fluticasone furoate 200 mcg once-daily, or placebo intranasally for 8 days. AR symptoms were induced during 4-hour allergen challenges with grass pollen in the VCC at the end of each 8-day treatment period. A first challenge was conducted at 1–5 hours post-dose, followed by a second challenge at 22–26 hours post-dose. The primary endpoint was total nasal symptom score (TNSS; sum of itch, sneeze, rhinorrhoea, obstruction symptoms assessed on a categorical scale of 0–3) weighted mean over 2–5 hours post-dose.

Results: Fluticasone furoate showed consistent attenuation of AR symptoms in both the early and late challenges. Compared with placebo, weighted mean of TNSS was reduced on average by 4.14 point-scores at 2–5 hours post-dose and 3.63 point scores at 23–26 hours post-dose. These positive effects were also seen across all secondary endpoints.

Conclusion: An 8-day treatment course of intranasal FF 200 mcg given once-daily statistically significantly reduced symptoms of AR including associated eye symptoms. Secondary endpoints included: TNSS weighted mean over 23–26 hours post-dose and global symptom score, eye symptom score, nasal secretions and nasal airflow weighted means over 2–5 and 23–26 hours post-dose. Fluticasone furoate showed consistent attenuation of AR symptoms in both the early and late challenges. Compared with placebo, weighted mean of TNSS was reduced on average by 4.14 point-scores at 2–5 hours post-dose and 3.63 point scores at 23–26 hours post-dose. These positive effects were also seen across all secondary endpoints.

Introduction

The allergen challenge model has regularly been used to evaluate the efficacy of antihistamines, nasal decongestants and some other treatments for allergic rhinitis1–5. Corticosteroids are a highly effective anti-inflammatory therapy in allergic conditions such as asthma and rhinitis, but hitherto there have been
few studies using glucocorticosteroids in the Vienna Challenge Chamber (VCC). The VCC offers a controlled and controllable paradigm in which to reproducibly evaluate the effect of medication on allergic rhinitis. This model allows the control of environmental conditions and therefore can eliminate some of the confounding factors encountered in normal outdoor studies such as the variability of the general environmental allergen load, variability in patients’ personal habits with respect to time spent indoors during the allergen season, or occurrence of concomitant respiratory tract infections.

Fluticasone furoate is a novel enhanced affinity glucocorticoid being developed as an intranasal steroid for the treatment of allergic rhinitis. Fluticasone furoate is a very potent glucocorticoid agonist showing the highest affinity for the human glucocorticoid receptor (GR) of all the clinically used glucocorticoids. This highly lipophilic molecule displays enhanced affinity for the target tissue, very high plasma protein binding and substantial selectivity over the other steroid hormone receptors (androgen, progesterone, oestrogen, mineralocorticoid), properties which would be expected to lead to a sustained duration of efficacy and to minimise systemic side-effects respectively. Very efficient hepatic inactivation is conferred by removal of the 17β-thioester functionality resulting in an inactive metabolite and negligible oral bioavailability. An X-ray crystal structure of the compound in the ligand binding domain of GR reveals that the molecule is particularly well accommodated in the receptor with the 17α-furoate ester moiety fully occupying the lipophilic 17α-pocket combined with strong interactions between receptor amino acid residues and the fluticasone backbone. The 17α-furoate ester however is metabolically stable and therefore the species fluticasone is not produced in the body. The properties of this new glucocorticoid would be predicted to lead to high levels of safety and efficacy and a sustained duration of anti-inflammatory action in man.

The purpose of the present study was to provide evidence for intranasal efficacy and for 24-hour duration of action of fluticasone furoate by evaluating its effects at 200 mcg administered intranasally once daily for 8 days versus placebo on symptoms of allergic rhinitis. These symptoms were elicited by two allergen challenges, the first one commencing 1 hour after the last dose (day 8) and the second one commencing 22 hours after the last dose (day 9).

The study was approved by the ethics committee of the ‘Institut für Hypertoniker’ in Vienna and was conducted in accordance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and all applicable regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki.

Patients and methods

Patients

Fifty-nine healthy male patients with a history of grass pollen allergic rhinitis were recruited for the study. After giving informed consent they were randomised and exposed to study medication. Fifty-five patients completed both treatment periods.

A patient was eligible for inclusion in this study only if all of the following criteria applied: (1) male (there were insufficient data on reproduction toxicology at the time of the study to permit the inclusion of females); (2) healthy (defined as free from clinically significant illness or disease as determined by their medical history, physical examination, laboratory studies and other tests besides allergic rhinitis); (3) aged 18–50 years; (4) had a history of grass pollen allergic rhinitis (free of symptoms at study start); (5) had a history of using non-steroidal anti-allergy medications during the season; (6) exhibited a moderate response to 1500 grass pollen grains/m³ within 2 hours in the VCC (which is defined as a nasal symptom score of at least 6); (7) had a positive skin prick test (wheal ≥4 mm) for grass pollen at or within the 12-months preceding the screening visit; (8) had a positive radio-allergosorbent test (RAST) (≥class 2) for grass pollen at or within the 12-months preceding the screening visit (subjects with sensitisations to other allergens were not included); (9) had a baseline forced expiratory volume in 1 second (FEV₁) ≥80% predicted and a baseline FEV₁/forced vital capacity (FVC) ≥70% predicted (using ECCS [European Community for Coal and Steel] reference values); and (10) had a body mass index (BMI) within the range 19–29 kg/m². Patients with any structural nasal abnormalities or nasal polyposis, a history of frequent nosebleeds, recent nasal surgery or recent (within 3 weeks) or ongoing upper respiratory tract infection, history of drug allergy, participating in ongoing or recently completed (within 4 months) any clinical study were excluded.

Study design

The study was a single-centre, randomised, double-blind, placebo-controlled, two-period crossover study, scheduled out of grass pollen season.

Patients underwent screening at least 14 days prior to the first dosing period to ensure that they were eligible to take part in the study. There were two treatment periods, each 9 days in duration.
Each treatment period was separated by a period of at least 14 days in order to ensure an adequate washout period for fluticasone furoate. Patients were randomised to receive either fluticasone furoate or placebo in Period 1, switching over to the other treatment in Period 2, according to the randomisation schedule. The randomisation schedule was generated within PACT (Patient Allocation for Clinical Trials), the legacy GlaxoSmithKline randomisation system. Subjects were allocated to the two treatment sequences (fluticasone furoate/placebo or placebo/fluticasone furoate). A block size of 4 was used when generating the randomisation schedule. Treatments were administered once daily for 8 days. The first dose (day 1) was administered in the unit in order to ensure adequate technique. Medication was issued to the patients for self-administration at 08:00 hours on days 2–7 of each treatment period. On day 8 of each treatment period, the patients had to undergo supervised administration of study medication at approximately 11:00 hours. At the end of each treatment period patients underwent two pollen allergen challenges lasting 4 hours in the VCC in order to elicit symptoms of allergic rhinitis. The pollen mix used consisted of *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense* and *Poa pratensis* in equal parts. The first challenge started 1 hour after the last dose (day 8) and the second challenge started 22 hours after the last dose (day 9). At least 3 days and no more than 10 days following the last dose of study medication a follow-up visit was performed.

**Allergen challenge**

Patients were pre-screened in order to ensure that they demonstrated threshold symptoms in response to a fixed allergen load. The VCC accommodated up to 20 patients in one sitting, all of whom were under constant supervision by medical staff outside the chamber. The chamber was charged with fresh air, which was cleaned, cooled, dried and then loaded with a qualitatively and quantitatively determined allergen load. Allergen concentration was monitored every 5 minutes, temperature, CO₂ and humidity were monitored every 5 seconds, allowing for a constant humidity (40%), temperature (24°C) and allergen load (1500 grains/m³) to be maintained (within ±5%) throughout the entire exposure period. These conditions were selected to simulate those found outdoors on a typical warm Austrian summer’s day.

**Efficacy assessments**

The severity of symptoms of allergic rhinitis was assessed at regular intervals during the course of the challenges. Nasal symptoms (sneeze, itch, rhinorrhea and obstruction), eye symptoms (watery eyes, itchy eyes, red eyes) and other symptoms (cough, itchy throat, itchy ears) were scored on a categorical scale at screening, pre-dose on day 1 and every 15 minutes during the challenges on days 8 and 9. Each of the symptoms was measured on a categorical scale of 0–3 (0 representing no symptoms and 3 representing severe symptoms). Secretion weight (a surrogate of nasal secretion measured by weighing tissues) was measured at screening and every 30 minutes during the challenges on days 8 and 9. Nasal airflow resistance (measured using active anterior rhinomanometry) was monitored at screening, pre-dose on day 1 and every 30 minutes during the challenges on days 8 and 9.

**Safety assessments**

Adverse event profile, spirometry, electrocardiogram (ECG) data (including PQ, QT, QTc and QRS interval), vital signs (heart rate, systolic and diastolic blood pressure) and laboratory parameters (haematology, clinical chemistry and urinalysis) were assessed at regular intervals.

**Statistical methods**

**Sample size**

Approximately 80 patients were to be screened to allow for 60 patients to be enrolled. This sample size was based upon the sample size used in previous rhinitis efficacy studies conducted at the Vienna unit. No formal sample size calculation was performed for this study, primarily due to insufficient information regarding variability or magnitude of response of anti-inflammatory therapies in the model proposed with this design.

**Populations**

The ‘All Patients’ population was defined as all patients randomised to treatment who received at least one dose of study treatment. This population was used for all listings and summaries of the safety data. The ‘Modified Per Protocol’ population included all patients who completed the study without major deviations from the protocol. Major deviations included non-compliance with study drug on greater than 2 days and use of disallowed concurrent medication. A disallowed medication was defined as a corticosteroid, long acting anti-histamine or short acting anti-histamine taken within 48 hours prior to the challenge. This population was used for all efficacy analyses.
**Endpoints**

The primary endpoint of interest was the weighted mean TNSS over 1–4 hours post-start of challenge (2–5 hours post-dose) on day 8. Secondary endpoints of interest included weighted mean TNSS 1–4 hours post start of challenge (23–26 hours post-dose) on day 9, weighted mean eye symptom scores, weighted mean other symptom scores, weighted mean global symptom scores, weighted mean nasal flow, weighted mean wet tissue weight 1–4 hours post start of challenge (2–5 hours or 23–26 hours post-dose) on days 8 and 9, respectively.

**Analysis**

The following combined symptom score endpoints were derived from the individual symptom scores at each relevant timepoint:

- TNSS (sum of obstruction, itch, sneeze and rhinorrhoea scores).
- Eye symptom score (sum of watery eyes, itchy eyes and red eyes).
- Other symptom scores (sum of cough, itchy throat, itchy ears).
- Global symptom score (sum of TNSS, eye symptom score and other symptom scores).

Weighted means were then derived over 1–4 hours post start of challenge on days 8 and 9 for TNSS, eye symptom score, global symptom score, nasal secretion and nasal airflow. The weighted mean was derived by calculating the area under the curve (AUC) – using the linear trapezoidal method – and then dividing the AUC by the relevant planned time interval.

Each of the weighted mean endpoints for each time range and day were analysed separately using a mixed effects model. The factors treatment and period were fitted as fixed effects and patient was fitted as a random effect. Baseline (pre-challenge on the relevant day) was fitted as a continuous covariate (fixed effect). The model assumptions were checked to assess whether a log transformation of the endpoints was required prior to analysis. A log transformation of the data was not considered necessary. The difference between the adjusted means for the two treatments was calculated along with the associated two-sided 95% confidence interval (CI) – calculated using the pooled estimate of variability – for each endpoint. Hypothesis tests were not formulated prior to the study and as a result p-values have not been presented. As an alternative, an estimation approach was adopted by interpreting the results using the two-sided 95% CIs from which both statistical significance and variability can be determined. Statistical significance was declared if the relevant CI did not contain zero. A value of zero indicates no treatment difference.

No formal statistical analyses of the safety data (adverse events, clinical laboratory parameters, vital signs, ECG and FEV₁ data) were performed.

All statistical analyses were performed using SAS version 8.2 (SAS Institute, North Carolina, USA) on a UNIX platform.

The patients who withdrew prematurely from the study were included in the analyses where data was available. Data collected at unscheduled time points were not used to calculate any of the derived parameters.

**Results**

**Study population**

All patients enrolled were Caucasian. Their mean (range) age was 26.8 years (21–43 years) and their mean (range) BMI was 22.91 kg/m² (19.4–29.0 kg/m²). All patients had a history of grass pollen induced allergy symptoms confirmed by positive skin prick test and/or positive RAST and moderate response in the VCC. They were not sensitised or did not have symptoms due to perennial allergens, e.g. house dust mite, cat, dog etc.

**Efficacy results**

Statistical significance was declared if the relevant two-sided 95% CI did not contain zero. A value of zero indicates no treatment difference (Table 1).

**Primary efficacy results**

A statistically significant mean reduction of −4.14 point-scores (approximately 56% decrease) was observed for the primary endpoint, weighted mean TNSS over 2–5 hours post dose (i.e. 1–4 hours post the start of challenge on day 8) when comparing fluticasone furoate with placebo (95% CI: −4.98 to −3.30 point scores).

**Secondary efficacy results**

A statistically significant mean reduction of −3.63 point scores (approximately 47% decrease) was also observed for the weighted mean TNSS over 23–26 hours post dose (i.e. 1–4 hours post the start of challenge on day 9) for fluticasone furoate versus placebo (95% CI: −4.44 to −2.82 point scores).

Figure 1 shows the mean TNSS over time. This figure further demonstrates that the improvement
in TNSS on fluticasone furoate was sustained until the 26 hour post dose evaluation.

The results of eye symptom scores, global symptom scores, nasal secretion weight and nasal airflow for fluticasone furoate versus placebo are also shown in Table 1. Ocular symptoms were improved with fluticasone furoate as were global symptom scores, nasal secretion weights and nasal airflow compared with placebo.

Improvements in symptom scores were seen for all other weighted mean combined symptom score endpoints (eye symptom scores, global symptom scores, nasal secretion weight and nasal airflow) over each of the time intervals on day 8 and 9.

Statistically significant mean reductions of $-2.03$ and $-1.68$ g (approximately 73% and 66% decreases) were observed for the weighted means of Nasal Secretion over 2–5 hours and 23–26 hours post dose for fluticasone furoate versus placebo (95% CIs: $-2.50$ to $-1.55$ g, $-1.55$ to $-1.33$ g), respectively.

Statistically significant mean increases of 176.6 and 116.2 mL/sec (approximately 23% and 16% increases) were observed for the weighted means of Nasal Airflow over 2–5 hours and 23–26 hours post dose.

### Table 1. Results of statistical analysis of weighted mean efficacy endpoints

<table>
<thead>
<tr>
<th>Day</th>
<th>Time interval post start of challenge (time post dose)</th>
<th>Weighted mean endpoint</th>
<th>Weighted mean endpoint</th>
<th>Adjusted means</th>
<th>Treatment difference (FF – placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1–4 hours (2–5 hours)</td>
<td>TNSS</td>
<td>3.30</td>
<td>7.44</td>
<td>-4.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eye symptom score</td>
<td>1.21</td>
<td>2.32</td>
<td>-1.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global symptom score</td>
<td>5.18</td>
<td>10.88</td>
<td>-5.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal secretion, g</td>
<td>0.75</td>
<td>2.78</td>
<td>-2.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal airflow, mL/sec</td>
<td>931.4</td>
<td>754.9</td>
<td>176.6</td>
</tr>
<tr>
<td>9</td>
<td>1–4 hours (23–26 hours)</td>
<td>TNSS</td>
<td>4.10</td>
<td>7.72</td>
<td>-3.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eye symptom score</td>
<td>1.70</td>
<td>2.57</td>
<td>-0.87</td>
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<tr>
<td></td>
<td></td>
<td>Global symptom score</td>
<td>6.62</td>
<td>11.31</td>
<td>-4.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal secretion, g</td>
<td>0.86</td>
<td>2.54</td>
<td>-1.68</td>
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<tr>
<td></td>
<td></td>
<td>Nasal airflow, mL/sec</td>
<td>866.1</td>
<td>749.9</td>
<td>116.2</td>
</tr>
</tbody>
</table>

*None of the CIs contain zero which suggest there is evidence of a statistically significant difference between treatments for all endpoints* 

CI = confidence interval; FF = fluticasone furoate; TNSS = total nasal symptom score

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**Figure 1. Summary of mean (95% CI) TNSS over time.** CI = confidence interval; FF = fluticasone furoate; TNSS = total nasal symptom score
for fluticasone furoate versus placebo (95% CIs: 106.3 to 246.8 mL/sec, 57.6 to 174.8 mL/sec), respectively. Figure 2 shows the mean nasal airflow over time. This figure further demonstrates that the improvement in nasal airflow on fluticasone furoate was sustained until the 26 hour post dose evaluation.

Safety results
Fluticasone furoate was well tolerated in all the patients. Only three adverse events were reported by two patients (3%), all of mild intensity. Two events were headache (reported by the same patient once during fluticasone furoate treatment period and once during placebo treatment period), and one event was nasal passage irritation (reported during the fluticasone furoate treatment period). Only the nasal passage irritation was deemed drug related by the investigator prior to unblinding. There were no clinically significant changes in vital signs, 12-lead ECGs, individual laboratory profiles and FEV1 measurements after nasal administrations of fluticasone furoate compared to baseline and placebo.

Discussion
This is the first study that has specifically assessed the efficacy of a novel glucocorticosteroid versus placebo in patients with grass pollen allergic rhinitis in the VCC. The design of the study is similar to that in previous studies with other allergic medications, e.g. antihistamines. The purpose of this study was to investigate the effects on rhinitis symptoms of an intranasal steroid currently under development, administered at a daily dose of 200 mcg for 8 days. To achieve this, a standardised allergen challenge model was used and the chosen dose was anticipated to produce clinical efficacy. Patients all previously diagnosed with allergic rhinitis to grass pollen but free of symptoms participated in two treatment periods. They were randomised to receive either fluticasone furoate or placebo in Period 1, switching over to the other treatment in Period 2, according to the crossover design of the study.

For all weighted mean endpoints (TNSS, eye symptoms, global symptoms, nasal secretion, nasal airflow), there was a rapid and steep response that peaked and plateaued one hour after the start of the challenge. It was clear that intranasal fluticasone furoate dramatically attenuated symptoms of allergic rhinitis induced by the allergen challenge when compared with placebo. That effect was reproduced 23–26 hours later during the second challenge, indicating that the beneficial effects of fluticasone furoate were sustained over 24 hours with respect to symptoms of allergic rhinitis. The responses were consistent across the endpoints. These results suggest that fluticasone furoate is a suitable candidate for a once daily steroid treatment in allergic rhinitis and as a result of this study the development programme for fluticasone furoate was initiated.
The dose chosen for this study, 200 mcg/day, had been well tolerated for up to 7 days repeat dosing in previous clinical studies with intranasal suspension formulations of fluticasone furoate. In preclinical studies, fluticasone furoate was found to have potency approximately twice that of fluticasone propionate and greater binding to respiratory tissue. As intranasal fluticasone propionate (FP) is a once daily treatment already the aim was to examine the potential for fluticasone furoate to demonstrate efficacy at 24 hours against placebo, and to reference against FP data from other studies. The 200 mcg/day (recommended FP daily dose) dose selected for this study provided the opportunity for these comparisons. However, a subsequent dose ranging study established that the optimum dose for fluticasone furoate is 110 mcg/day for adults and adolescents over 12 years of age.

The VCC is a well established validated model to evaluate the efficacy of antihistamines and other allergic treatments. Hitherto there have been no publications of randomised placebo-controlled trials with respect to evaluation of glucocorticoids in this model. A recent paper assessed the efficacy and safety of budesonide nasal spray in the management of nasal congestion in the VCC but it was not a placebo-controlled trial and the study was not blinded. Furthermore the challenge was conducted after a single dose only. However, in a previous study the efficacy of fluticasone propionate was demonstrated in this model. The results are not strictly comparable as the design was different.

It is difficult to compare these results with those published with H1-receptor agonists because of the differences in patients, design and analysis. Those data suggest a response curve that has a similar scattering to fluticasone furoate and several antihistamines investigated. However, the therapeutic response of fluticasone furoate was clearly superior to other drugs tested in the VCC before. Since other glucocorticoids have not been studied in this model, comparisons between fluticasone furoate and these other compounds is not possible at this time.

Conclusions

An 8-day course of 200 mcg of fluticasone furoate statistically significantly reduced symptoms of allergic rhinitis including associated eye symptoms elicited by an allergen challenge commencing one hour after dosing, compared with placebo. Statistical significance was declared where the relevant two-sided 95% CI did not contain zero. The positive effect is sustained over 24 hours suggesting that fluticasone furoate should be efficacious as a once daily medication in patients with allergic rhinitis. The results of this study confirm the value of the VCC in assessing the efficacy of intranasal steroids.

Acknowledgements

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