Efficacy and Safety of an Oral Formulation of Cetirizine and Prolonged-Release Pseudoephedrine versus Budesonide Nasal Spray in the Management of Nasal Congestion in Allergic Rhinitis

Ursula P. Ziegelmayer,1 Friedrich Horak,1 Josef Toth,1 Bernhard Marks,1 Uwe E. Berger1 and Bernard Burtin2

1 ENT - University Clinic Vienna, Vienna, Austria
2 UCB S.A., Braine-l’Alleud, Belgium

Abstract

Introduction: The aim of this study was to compare the decongestant properties and tolerability of oral cetirizine and pseudoephedrine in a prolonged release form with those of nasal (aqueous spray) budesonide.

Methods: Thirty-six individuals experiencing allergic rhinitis to house dustmites (HDM) participated in a study according to a randomized, crossover, two-period, two-treatment design with at least a 2-week washout period between treatments. In each period of 4 consecutive days, medications were taken twice daily. On day 1, immediately after the first intake of medication, individuals were exposed to HDM extract in the Vienna Challenge Chamber (VCC) for 5 hours. The primary efficacy parameter was nasal congestion, assessed by active anterior rhinomanometry and rating of nasal cavity photos.

Results: Rhinomanometry and nasal cavity photos both indicated that cetirizine/pseudoephedrine efficacy was statistically superior to budesonide in the management of nasal congestion during VCC sessions. The efficacy of cetirizine/pseudoephedrine was similar to that of budesonide from the end of day 1 up to day 4 when individuals were exposed to their natural environment post exposure to the allergens.

This study confirms the efficacy of cetirizine/pseudoephedrine and budesonide in the management of nasal congestion associated with allergic rhinitis. Both medications were well-tolerated. Cetirizine/pseudoephedrine was more effective than budesonide during HDM exposure, whereas budesonide became as effective as cetirizine/pseudoephedrine several hours post exposure to the allergens.

Traditional symptoms of allergic rhinitis include nasal congestion, sneezing, rhinorrhea, itchy nose, palate and/or throat, and itchy watery eyes.[1]

Antihistamine medications effectively treat symptoms associated with pollen allergy, but are less effective in reducing nasal congestion, the prominent symptom from home allergen (e.g., house dust-mites) exposure.[1] To optimize the treatment of allergic rhinitis, combinations of antihistamine and nasal decongestant have been shown to be more effective than either drug administered alone.[2-4]

Topical corticosteroids, among other therapies, are very effective in alleviating symptoms associated with allergic rhinitis.[1] The effects of topical corticosteroids on nasal congestion favor them above other treatments, especially when nasal obstruction is the predominant symptom in patients with allergic rhinitis.

The aim of this study was to compare the decongestant properties and tolerability of an oral formulation of cetirizine/
pseudoephedrine with those of a topical solution of budesonide, in the treatment of patients with allergic rhinitis.

Materials and Methods

Study Design

The study was carried out in accordance with the EU rules for Good Clinical Practice and consisted of a randomized, crossover, two-period, two-treatment design with at least a 2-week washout period between medications. During a period of 4 consecutive days, medications were administered twice daily in a non-blinded manner. On day 1 in each period, immediately after first medication intake, individuals were exposed to house dustmite (HDM) extract in the Vienna Challenge Chamber (VCC) for 5 hours. The VCC is a closed room in which up to 12 patients can be exposed to specific aeroallergens in well-controlled and reproducible conditions.

Thirty-six individuals allergic to HDM were randomly assigned to receive cetirizine/pseudoephedrine during period 1 and budesonide during period 2, or vice versa.

A history of allergy was confirmed by anamnesis and a positive radio allergen sorbent test or skin prick test to HDM carried out <1 year before enrolment. Female individuals of childbearing potential had to use an effective means of contraception during the study period.

Individuals were excluded from the study if they had a history of: (i) chronic disease such as diabetes mellitus, asthma, or epilepsy; (ii) renal, hepatic, or cardiac dysfunction; (iii) known allergy to cetirizine and other piperazines, pseudoephedrine, budesonide or their constituents; (iv) pregnancy or lactation; (v) increased intraocular pressure; (vi) urinary retention; (vii) known drug or alcohol addiction; or (viii) sinus infections requiring antibacterial treatment.

With the exception of oral contraceptives, the current or recent (<30 days) use of any prescribed medication (especially monoamine oxidase inhibitors or reserpine) was not permitted. Other medications not permitted for various periods of time prior to the start of the study included systemic corticosteroids (1 month), astemizole (6 weeks), topical corticosteroids (2 weeks), ketotifen (2 weeks), other antihistamines (7 days), sympathomimetics (1 day), and menthol (1 hour).

In the present study, conducted out of the pollen season, individuals were exposed to 70 ng/m³ dermatophagoides pteronyssinus extract I under controlled temperature (24°C) and humidity (30%). Temperature and humidity were regularly monitored and adjusted to maintain similar conditions during the challenge sessions.

Study Medications

Cetirizine/pseudoephedrine (one tablet containing 5 mg cetirizine and 120 mg pseudoephedrine [prolonged release granules] pseudoephedrine) was delivered as an oral capsule. Budesonide aqueous nasal spray (100 µg per nostril) was administered through a metered pump nasal spray. Both medications were taken twice daily at 8 am and 8 pm for 4 days.

During the VCC sessions, no rescue medication was allowed with the exception of β2-sympathomimetics in case of asthma symptoms.

Evaluations

On a regular basis during VCC sessions, nasal congestion was measured by active rhinomanometry. Nasal secretions were quantified by weighing of handkerchiefs. Nasal and ocular symptoms were assessed on a 4-point scale from 0 (no symptom) to 3 (severe discomfort). Global satisfaction was measured on a 0 mm (no discomfort) to 100 mm (severe discomfort) visual analog scale. Peak nasal inspiratory flow (PNIF) and PEF were also measured at medication intake on days 1–4 with the highest value among three attempts carried out at each assessment taken into consideration.

Nasal cavity photos recorded during VCC sessions were afterwards evaluated on a 7-point scale from −3 (maximal decrease of mucosal swelling) to +3 (maximal increase) in a blinded fashion by five independent ear, nose and throat specialists.

Systolic and diastolic blood pressures were recorded in a sitting position at the beginning and the end of each treatment period, on the same arm and after a rest of 5 minutes.

![Fig. 1. Evolution of the nasal airflow (anterior rhinomanometry) during the VCC sessions (baseline corrected). VCC = Vienna Challenge Chamber.](image-url)
Adverse events were continuously monitored during the VCC sessions and recorded on diary cards given to the participants. The diary cards were collected by the investigator at the end of each session.

Statistical Methods

The mean values of the efficacy parameters recorded during VCC sessions as well as the total amount of nasal secretions were computed. Mean PNIF and PEF measurements recorded during days 1–4 were also computed. The primary efficacy parameter was nasal congestion, assessed through rhinomanometry and rating of the nasal cavity photos. Statistical analyses were carried out according to the Koch’s non-parametric approach\(^6\) specific for two period crossover studies. All tests were two-tailed at the 5% level of significance.

Results

Thirty-six participants (16 females, 20 males) with a mean age of 25.7 years (SD 3.5 years), mean weight of 68.9kg (SD 11.1kg) and a mean height of 176.1cm (SD 9.4cm) were randomized to treatment and completed the study.

Evolution (corrected for baseline) of nasal airflow (cm\(^3\)/sec) during VCC sessions are provided in figure 1. Thirty minutes after starting the HDM challenge, similar reductions in nasal airflow were recorded for both medications. Beyond that timepoint, different patterns were observed. Over the 5-hour challenge, individuals treated with cetirizine/pseudoephedrine were significantly more protected against nasal airflow reduction than those treated with budesonide (−162.2 vs −237.5 cm\(^3\)/sec, p = 0.0255 [table I]).

The above findings are supported by the ratings of the nasal cavity photos; the increase of the mucosal swelling was found to be significantly less in individuals treated with cetirizine/pseudoephedrine compared to budesonide (0.76 vs 0.93 [mean score], p = 0.0386 [table I]).

In addition, all other efficacy parameters recorded during VCC sessions showed significantly greater improvement with cetirizine/pseudoephedrine compared to budesonide (table I).

Evolution of PNIF values during VCC sessions and from the end of day 1 to day 4 are presented in figure 2. Significant differences in favor of cetirizine/pseudoephedrine were noted during the VCC sessions; budesonide and cetirizine/pseudoephedrine displayed similar efficacy from the end of day 1 to

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cetirizine/ pseudoephedrine(^a)</th>
<th>Budesonide</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal congestion (mean reduction [cm(^3)/sec], baseline corrected)</td>
<td>−162.2 (182.8)</td>
<td>−237.5 (182.1)</td>
<td>0.0255</td>
</tr>
<tr>
<td>Nasal congestion (ENT ratings; mean rating score)</td>
<td>0.76 (0.43)</td>
<td>0.93 (0.52)</td>
<td>0.0386</td>
</tr>
<tr>
<td>Nasal secretions (sum in g during the 5hr session in the VCC)</td>
<td>12.5 (20.3)</td>
<td>20.8 (25.6)</td>
<td>0.0002</td>
</tr>
<tr>
<td>PNIF (mean value [L/min])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>challenge period</td>
<td>146.4 (67.1)</td>
<td>121.4 (65.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>following days (days 1–4)</td>
<td>165.9 (61.5)</td>
<td>161.8 (54.4)</td>
<td>0.4494</td>
</tr>
<tr>
<td>PEF (mean value [L/min])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>challenge period</td>
<td>521.1 (102.5)</td>
<td>509.2 (95.5)</td>
<td>0.0189</td>
</tr>
<tr>
<td>following days (days 1–4)</td>
<td>524.0 (101.8)</td>
<td>512.3 (99.6)</td>
<td>0.0055</td>
</tr>
<tr>
<td><strong>Subjective</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction (mean score)</td>
<td>1.04 (0.60)</td>
<td>1.33 (0.66)</td>
<td>0.0040</td>
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<tr>
<td>Rhinorhoea (mean score)</td>
<td>0.80 (0.65)</td>
<td>1.18 (0.71)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pruritus (mean score)</td>
<td>0.70 (0.58)</td>
<td>1.15 (0.68)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Sneezing (mean score)</td>
<td>0.38 (0.36)</td>
<td>0.75 (0.59)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ocular pruritus (mean score)</td>
<td>0.34 (0.39)</td>
<td>0.62 (0.64)</td>
<td>0.0129</td>
</tr>
<tr>
<td>Global satisfaction (VAS) [mean value (mm), baseline corrected]</td>
<td>4.61 (15.05)</td>
<td>13.97 (16.23)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

\(a\) Figures in this column correspond to better performances.

ENT = ear, nose, and throat; PNIF = peak nasal inspiratory flow; VAS = visual analog scale; VCC = Vienna Challenge Chamber.

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day 4. PEF measurements were significantly in favor of cetirizine/pseudoephedrine during and after VCC sessions (table I).

Seven participants reported 10 adverse events (7 with cetirizine/pseudoephedrine, 3 with budesonide) during the study. The investigator attributed all these events to HDM allergen and not to study medications. All events resolved completely at the end of the study. No serious adverse events were reported.

Blood pressure recordings did not show a difference between medications; no hypertension was observed.

Discussion

During HDM exposure in the VCC, immediately after medication intake, a consistent and sustained relief of nasal congestion was observed with cetirizine/pseudoephedrine. All other efficacy parameters were statistically in favor of cetirizine/pseudoephedrine. These results were in agreement with those reported in two previous studies.\(^7,8\) Efficacy of both medications were similar when individuals were exposed afterwards to their natural environment from the end of day 1 until day 4.

In this study, the techniques used to assess nasal congestion and other efficacy parameters are all well-known standards. The use of a study design similar to the one used in two previous studies\(^7,8\) allowed direct between-treatment comparisons. The possibility to blind the study using double-dummy preparations was discarded as primary efficacy parameters were derived from objective measurements (rhinomanometry) or from blinded ENT specialists (rating of photos).

Pharmacological therapies for allergic rhinitis include decongestants, antihistamines, anticholinergics, intranasal sodium cromolyn (sodium cromoglicate) and intranasal corticosteroids taken separately or in combination. For each of these treatment options, effective outcome requires that allergic individuals and physicians work in close partnership. Patients need to be educated about the administration, benefits, and risks of the medications.

The widespread use of intranasal budesonide over several years has become an established treatment for allergic rhinitis.\(^9\) As with other corticosteroids, the maximal effect of budesonide is not reached immediately. The results of the present study show that for budesonide, PNF improvements started to be relevant and similar to those reported with cetirizine/pseudoephedrine only at the end of day 1 and beyond (figure 2). This finding is consistent with the 5 hours onset of action reported for budesonide.\(^10\)

PEF measurements during VCC sessions were significantly better with cetirizine/pseudoephedrine than budesonide; PEF values remained significantly superior to those reported for budesonide from end of day 1 to end of day 4. The latter findings may be related to the low systemic availability of budesonide.

Hypertension has been reported with pseudoephedrine in some uncontrolled studies. In the present study, the absence of any relevant blood pressure effects with the slow release formulation indicates that this formulation of pseudoephedrine is well tolerated.
Conclusion

This study confirms the efficacy of cetirizine/pseudoephedrine and budesonide in the management of nasal congestion associated with allergic rhinitis. Cetirizine/pseudoephedrine has the potential to fill the gap between the rapid onset of action but short-lived effect of vasoconstrictor drugs $\alpha$-adrenoceptor agonists like ephedrine, xylometazoline and oxymetazoline and the well-known but delayed efficacy of corticosteroids in the treatment of allergic rhinitis.

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References


Correspondence and offprints: Dr Friedrich Horak, ENT - University Clinic Vienna, Währinger Gürtel, 18 – 20, A-1090 Vienna, Austria.
E-mail: friedrich.horak@vienna.at