Efficacy and Safety of an Oral Formulation of Cetirizine and Prolonged-release Pseudoephedrine versus Xylometazoline Nasal Spray in Nasal Congestion

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Summary

The aim of this study was to compare the decongestant properties and tolerability of the sympathomimetic xylometazoline hydrochloride 0.1% (CAS 1218-35-5, XMZ) and an oral formulation of cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg (CAS 83881-51-0 and 90-82-4, CTZ/PSE; Cirrus®). Thirty-six asymptomatic patients suffering from perennial allergic rhinitis from house dust mite were randomized to this open two-period crossover study. Patients received the study medications for four days each. In each period, treatments were taken twice a day. On day 1 in each period, immediately after the first dose of medication, patients were challenged with Dermatophagoides pteronyssinus extract 1 in the Vienna Challenge Chamber for 5 h. Primary efficacy parameters were nasal congestion evaluated by digital analysis of nasal cavity photographs and nasal airflow. Furthermore, amounts of nasal secretions, nasal and ocular symptoms were recorded. In addition, 5 independent Ear-Nose-Throat specialists also assessed nasal cavity photographs. Statistical analyses were conducted at the 5% level of significance.

Key words
- CAS 90-82-4
- CAS 1218-35-5
- CAS 83881-51-0
- Cetirizine
- Cirrus®
- Nasal congestion, digital imaging
- Pseudoephedrine
- Xylometazoline

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Zusammenfassung

Wirksamkeit und Verträglichkeit einer oralen Kombination von Cetirizinund Pseudoephedrin versus Xylometazolin-Nasenspray bei nasaler Blockade


Mit Ausnahme der nasalen Blockade war die Stärke aller subjektiven Symptome bei CTZ/PSE signifikant geringer und das Allgemeinbefinden signifikant besser.

Die Menge an produziertem Nasensekret war unter der Therapie mit CTZ/PSE ebenfalls signifikant niedriger.

1. Introduction

Nasal congestion is a prominent symptom in patients suffering from common cold, allergic and non-allergic rhinitis, or with nasal or sinus disease [1]. Although these disorders are not life threatening, they are responsible for substantial discomfort and impaired quality of life [1]. Increases and decreases in nasal patency are dependent on changes in the sympathetic innervation of the venous sinusoids (normally held in a half-maximal contractile state), and relief of symptoms may be obtained with topical or oral sympathomimetic decongestants. Topical decongestants have the advantage of a selective area of action and a rapid onset of action [2].

Available products commonly contain xylometazoline or oxytetraxoline, sympathomimetic vasoconstrictor agents synthesized from naphazoline [3]. Although these compounds do not alleviate sneezing or nasal discharge, they effectively reduce the supply of blood to, and the extent of edema of the nasal mucosa [1]. However, these agents are recommended for periods not exceeding 5 to 7 days, as their overuse may be associated with rebound swelling of the mucosa caused by down-regulation of α-adrenergic receptors on the nasal vasculature [2, 4]. The rebound stuffiness may be alleviated by further and progressively higher doses of medication; this may lead to the patient's dependence on the drug and the establishment of a vicious circle that may result in habituation and the condition of rhinitis medicamentosa [5].

Oral decongestants, which are not associated with rebound nasal congestion [4], may contain only vasoconstrictors, such as the sympathomimetic amines pseudoephedrine, phenylephrine or phenylpropanolamine, or a decongestant combined with an antihistamine. When used alone, antihistamines are associated with low efficacy in nasal decongestion [1]. However, they reduce nasal vascular permeability and mucus production, and well designed clinical studies have shown efficacy and synergism of oral sympathomimetic amines in combination with antihistamines in the treatment of nasal congestion caused by infection or allergy [6].

Cetirizine is a potent second-generation H1-antagonist that does not appear to be associated with the adverse central nervous system and anticholinergic effects seen with first-generation agents, such as chlorpheniramine and diphenhydramine [4, 7–9]. It considerably reduces sneezing, nasal pruritus and rhinorrhea when used alone in patients with perennial or seasonal rhinitis at a dosage of 10 mg/day [10–13]. Pseudoephedrine is an effective oral decongestant with a rapid onset of action. Its properties are similar to those of ephedrine, but it has less pronounced sympathomimetic effect [4]. A combination of cetirizine 5 mg and prolonged-release pseudoephedrine 120 mg given twice a day has been shown in a placebo-controlled, randomised, crossover study to be effective in the relief of nasal congestion [14]. Combination therapy with the two agents has also been shown to be more effective than
either agent administered alone in the treatment of perennial allergic rhinitis [15].

The aim of this study was to compare the clinical efficacy of the combination of cetirizine and pseudoephedrine (CAS 83881-51-0 and 90-82-4, CTZ/PSE) with xylometazoline 0.1 % nasal spray (CAS 1218-35-5, XMZ) in terms of reducing nasal congestion. Topical xylometazoline was chosen as comparator because it is an effective nasal decongestant with a rapid onset of action [16]. On this behalf a house dust mite challenge (HDM) in the Vienna Challenge Chamber (VCC) was accomplished.

Medications were administered no more than for 4 consecutive days to avoid any possibility of discomfort caused by rebound congestion associated with the use of the nasal spray.

2. Materials and methods

2.1. Study design

The study was approved by the Ethics Committee of the University of Vienna and was carried out in accordance with the Declaration of Helsinki. European Union rules for Good Clinical Practice and local legislative requirements were followed. Written informed consent was obtained from each patient.

Study was conducted according to a randomized, crossover two-period two-treatment design. Treatments were delivered in a non-blind way. In each period of 4 consecutive days, treatments were taken twice daily (every 12 h). A washout of at least 2 weeks was observed between the 2 periods. On day 1 in each period, immediately after the first dose of medication, patients were challenged in the VCC during 5 h.

A total of 36 patients, aged between 18 and 55 years and suffering from perennial allergic rhinitis (PAR) caused by HM were assigned to receive either CTZ/PSE in period 1 and XMZ in period 2 or the opposite: XMZ followed by CTZ/PSE. Study was conducted out of the pollen season.

The history of perennial allergic rhinitis (PAR) was confirmed by anamnesis and a positive Radio Allergo Sorbent test or skin prick test to HM carried out within the year before enrolment. Female patients with childbearing potential had to use an effective means of contraception.

Excluded were patients with chronic disease such as diabetes mellitus, asthma or epilepsy; renal, hepatic or cardiac dysfunction; known allergy to cetirizine and other pipenzines, pseudoephedrine, xylometazoline, or their constituents; pregnant and lactating women. Patients with increased intraocular pressure, urinary retention, known drug or alcohol addiction or with sinus infections requiring antibacterial treatment were also excluded.

With the exception of oral contraceptives, the current use or use within the 30 days before enrolment of any prescribed medication (particularly monoamine oxidase inhibitors or serpine) was not permitted. No rescue medication was allowed in the study. However, use of β₂-sympathomimetics was allowed for patients who developed asthma symptoms during the VCC sessions (day 1 in each period). Other exclusion periods before the start of the study were methyl (1 h), ketotifen (2 weeks), astemizole (6 weeks), other antihistamines (7 days), sympathomimetic agents (1 day), topical corticosteroids (2 weeks) and systemic corticosteroids (1 month).

The VCC is a closed room with windows, chairs, a ventilation system and communication equipment in which up to 12 patients can be exposed in a well-controlled and reproducible way to specific allergens. It complies with the recommendations for specific challenge rooms of the Subcommittee on Bronchoprovocation of Occupational Asthma [17]. In the present study, patients were exposed for 5 h to 110 ng/m³ Dermapthogoides pteronyssinus extract I (Der p I) under controlled temperature (24 °C) and humidity (30 %). Concentration of Der p I was monitored at 5-min intervals. During the VCC sessions, standard efficacy and safety parameters were measured on a regular basis.

2.2. Study medications

Treatments administered were oral capsules of cetirizine 5 mg and pseudo-ephedrine 120 mg in a prolonged-released form (Cirrus®; test preparation batch no. 78, expiry date 6/97, Manufacturer UCB S.A., Braine l’Alleud, Belgium) and xylometazoline 0.1 % nasal spray (reference preparation, batch no. 029601, expiry date 12/00, received from pharmacy). The study medications were taken twice daily at 8:00 and 20:00 h (one oral capsule or 1 puff in each nostril).

2.3. Evaluations

Nasal congestion evaluated by digital analysis of the nasal cavity photographs and nasal airflow measured by active anterior rhinomometry were defined as primary parameters. Ratings of the nasal cavity photographs by 5 independent Ear-Nose-Throat (ENT) specialists, amounts of nasal secretions, nasal and ocular symptoms, global evaluation as well as peak nasal inspiratory flow rate (PNIF) were considered as secondary parameters. Tolerability was recorded at the beginning and the end of each period and continuously during the VCC sessions. Peak expiratory flow rate (PEF) and blood pressure were also recorded.

Nasal congestion (digital units and ratings) was assessed in two ways: digital analysis of the photographs of the nasal cavity and rating of these photos by 5 independent ENT specialists. Photographs of the nasal airflow cavity were carried out at times 0, 0.5, 1, 3 and 5 h in each VCC session. Photos were obtained from a video endoscope (Wolf, Gleichen, Germany) and a cold-light source (Highlight 3000, Olympus Optical Co., Hamburg, Germany). During the investigation of the nasal cavity, patients head was stabilized into a modified slit lamp base, microscope of the slit lamp base was replaced by the endoscope. Coordinates of the endoscope position for each patient were recorded in order to reproduce similar positions at each investigation. Images from the endoscope were sent to a digital frame grabber (Matrix Magic, modified by Galai, Olympus Optical Co., Hamburg, Germany), digital information was stored onto a personal computer. The density of black information (free airway) in the digital images was analyzed using the WCUE-3 software (Olympus Optical Co., Hamburg, Germany), results were expressed in digital units, a higher value indicating a lower congestion. Additionally, changes from baseline in mucosal swelling (individual photographs) were also assessed (ratings) by 5 independent ENT specialists on a 7-point scale ranging from −3 (maximal decrease of the mucosal swelling) to +3 (maximal increase).

Nasal airflow (cm³/s) was measured at the start and every 30 min in each VCC session by active anterior rhinomometry at a sample pressure of 150 Pascal (RhinoTest MP441, Allergopharma, Hamburg, Germany).
Nasal secretion (g): Amounts of nasal secretions were assessed every 30 min in each VCC session by weighing standard handkerchiefs provided to the patients.

Nasal and ocular symptoms (score): Severity of subjective symptoms (ocular pruritus, rhinorrhea, nasal obstruction, sneezing and nasal pruritus) was assessed by the patients on a 4-point scale ranging from 0 (no symptom) to 3 (severe discomfort) every 15 min during the VCC sessions.

Global evaluation (mm): Global condition was assessed by the patients on a 100mm visual analogue scale (VAS) every 15 min during the VCC sessions; on this scale, 0 mm corresponds to “no discomfort” and 100 mm to an “extreme discomfort”.

PNIF and PEF (l/min): PNIF and PEF were recorded at the time of treatment administration (8:00 and 20:00 h) on days 1 to 4 in each period and every 30 min during the VCC sessions. At each assessment, only the highest value amongst 3 attempts was considered. Appropriate devices were used (Epipharm allergy service, Leonding, Austria).

Blood pressure (mm Hg): Sitting systolic and diastolic blood pressures were recorded at the beginning and the end of each period.

2.4. Statistical methods

Areas under the parameter-versus-time curves (AUC) were computed for nasal congestion (digital units) and nasal airflow using the linear trapezoidal rule. In addition, sum of PNIF and PEF measurements (challenge period, 4 following days), sum of nasal secretions, sum of scores for each nasal and ocular symptom, as well as the sum of scores for all the nasal symptoms were also computed. Statistical analyses were carried out according to the two periods – two-treatment crossover design of the study [22]. All tests were two-tailed at the 5% level of significance. From a previous study [14], it was computed that 2 sequences of 15 patients would allow to differentiate, with a power of 80%, the medications if their activities differ by more than 13% as measured by nasal congestion.

3. Results

Thirty-six PAR patients (18 males, 18 females) with a mean age (± SD) of 25.7 (± 4.7) years, mean weight of 68.2 (± 12.7) kg and a mean height of 174.6 (± 10.0) cm were randomized. Out of them, 5 withdrew during the study: 2 for personal reasons, 3 because of adverse events (uveitis in 1 patient who had received CTZ/PSE; moderate to severe late phase reactions in 1 CTZ/PSE-treated patient and 1 XMZ-treated patient). Efficacy analyses were carried out on the 31 patients who completed the study; safety analyses considered the 36 randomized patients.

Nasal congestion (digital units): Evolutions of the nasal congestion (corrected for baseline) during the VCC sessions are provided in Fig. 1. Areas under the curves (sum of the right ad left nostrils) computed from the digital images analyses show no overall significant difference between XMZ and CTZ/PSE (0.09 vs. -3.01 digital units × h, p = 0.842, Table 1). XMZ-curve points out the rapid decrease of nasal congestion observed with this medication within the first 30 min of chal-

Table 1: Efficacy results for the objective and subjective assessments (mean value ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cetirizine/ pseudophedrine (CTZ/PSE)</th>
<th>Xyloros/atalin (XMZ)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective parameters</strong></td>
<td></td>
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<tr>
<td>Nasal congestion (ENT ratings)</td>
<td>20.6 (± 17.1)</td>
<td>9.5 (± 22.7)</td>
<td>0.008</td>
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<tr>
<td>(sum of ratings)</td>
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<tr>
<td>Nasal congestion (digital analysis)</td>
<td>-3.01 (± 67.41)</td>
<td>0.09 (± 75.58)</td>
<td>0.8417</td>
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<tr>
<td>(AUC – baseline corrected)</td>
<td></td>
<td></td>
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<tr>
<td>Nasal airflow (rhinomanometry)</td>
<td>-803.8 (± 783.8)</td>
<td>-455.1 (± 989.3)</td>
<td>0.1642</td>
</tr>
<tr>
<td>(AUC – baseline corrected)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNIF (sum of values (l/min))</td>
<td>1570 (± 724)</td>
<td>1592 (± 722)</td>
<td>0.774</td>
</tr>
<tr>
<td>Challenge period</td>
<td>1157 (± 468)</td>
<td>1012 (± 422)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Following days</td>
<td>11.9 (± 15.4)</td>
<td>22.2 (± 21.0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Nasal secretions (g)</td>
<td>5633 (± 1346)</td>
<td>5492 (± 1285)</td>
<td>0.039</td>
</tr>
<tr>
<td>(sum of values (l/min))</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Challenge period</td>
<td>3612 (± 833)</td>
<td>3510 (± 799)</td>
<td>0.044</td>
</tr>
<tr>
<td>Following days</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Subjective parameters</strong></td>
<td></td>
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<tr>
<td>Sum of nasal symptoms</td>
<td>69.4 (± 50.2)</td>
<td>101.6 (± 51.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Obstruction</td>
<td>18.8 (± 14.1)</td>
<td>18.2 (± 14.4)</td>
<td>0.8949</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>19.5 (± 15.7)</td>
<td>30.0 (± 16.8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Itching</td>
<td>19.3 (± 15.0)</td>
<td>30.5 (± 18.6)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Sneezing</td>
<td>11.8 (± 12.5)</td>
<td>22.9 (± 14.6)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Itching eyes score</td>
<td>6.1 (± 8.6)</td>
<td>14.2 (± 13.6)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Global impression (VAS)</td>
<td>402.2 (± 333.3)</td>
<td>658.0 (± 439.2)</td>
<td>0.0005</td>
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</tbody>
</table>
lenge. After 30 min this effect disappears progressively, falling below that of CTZ/PSE after approximately 2.5 h. On the opposite, CTZ/PSE is associated with a small increase of the nasal congestion within the first 30 min of challenge. After 30 min, nasal congestion levels converge towards those observed before starting the challenge (baseline values). These results concur with nasal airflow results described below.

Nasal airflow (cm$^3$/s): Evolutions of nasal airflow (corrected for baseline) during the VCC sessions follow a pattern similar to the evolutions of nasal congestion (digital units) depicted in Fig. 1. No significant difference are observed between the AUC under CTZ/PSE and XMZ (-803.8 vs. -455.1 (cm$^3$/s) × h, $p = 0.164$, Table 1).

Nasal congestion (ratings): Assessments of the mucosal swelling by ENT specialists are in favor of XMZ as compared to CTZ/PSE (9.5 vs. 20.6, $p = 0.008$, Table 1). The strong and rapid decrease observed in nasal congestion within the 30 min after XMZ administration probably explains these assessments.

Nasal secretion (g): Amounts of nasal secretions in each VCC session are significantly lower with CTZ/PSE than with XMZ (11.9 vs. 22.17 g, $p < 0.001$, Table 1).

Nasal and ocular symptoms (score): With the exception of nasal obstruction (no difference between CTZ/PSE and XMZ; Fig. 2), severity measured for all the nasal and ocular symptoms is in favor of CTZ/PSE as compared to XMZ (all $p$ values < 0.001, Table 1). Sum of scores over all the nasal symptoms is also more favorable with CTZ/PSE than with XMZ (69.4 vs. 101.6, $p < 0.001$, Table 1).
Global evaluation (mm): Evolutions of the global condition during the VCC sessions are given in Fig. 3. As expected from the results recorded for nasal and ocular symptoms, CTZ/PSE appears globally (AUC) to provide a better comfort than XMZ (402.2 vs. 658.0 mm x h, p < 0.001, Table 1).

PNIF and PEF (l/min): No relevant difference between CTZ/PSE and XMZ are observed during the VCC sessions for these parameters. However, the values recorded from end of day 1 to day 4 show that PNIF as well PEF are in favor of CTZ/PSE as compared to XMZ (PEF: 3612 vs. 3510 (l/min), p = 0.044, Table 1, Fig. 4; PNIF: 1157 vs. 1112 (l/min), p < 0.001, Table 1, Fig. 5).

Tolerability: Out of the 36 patients randomized in the study, 21 patients (5 CTZ/PSE-patients, 15 XMZ-patients and 1 patient during the washout period) reported 21 adverse events. All reported events except one resolved completely after the study; unresolved event, which led to treatment withdrawal, was a single case of uveitis (cause unknown) reported towards the end of the washout period after CTZ/PSE. It was deemed unlikely that this event was related to the medication. Overall, CTZ/PSE showed superior tolerability to XMZ, with 5 events (3 in period 1 and 2 in period 2) and 15 events (9 in period 1 and 6 in period 2) being reported, respectively (Table 2). The most common adverse event was due to the HDM challenge: mild to moderate bronchospasm; this was reported by 9 patients, 7 of whom while receiving XMZ. No serious adverse events were reported.

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

4. Discussion

Topical nasal decongestants have the advantage of a rapid onset of action [2]. Data recorded with XMZ 0.1 % nasal spray in this study are in agreement with this property. However, this advantage seemed to be relatively short-lived with a decline of the decongestant effect appearing already after 30 min. In contrast, the consistent activity observed with the systemic CTZ/PSE combination, noticeable 30 min after administration, was maintained for a period of at least 5 h as demonstrated by the analysis of the digital images and the rhinomanometry measures. PNIF results, although less reproducible than the standard techniques of rhinomanometry, support this longer activity of CTZ/PSE as compared to XMZ.

The principal objection to the use of topical sympathomimetic agents relates to their tendency to cause rebound congestion, possibly linked to downregulation of α-adrenergic receptors [2]. Rhinitis medicamentosa was found to develop within 10 days in healthy volunteers receiving oxymetazoline nasal spray [3], which confirms recommendations that these agents are suitable for short-term use only. Furthermore, most nasal drops and sprays contain a preservative, commonly benzalkonium chloride, which has been reported to cause tissue damage [19] and to aggravate rebound nasal congestion [20]. These problems may be circumvented by the use of systemic adrenergic agonists although these agents have been linked with systemic adverse effects, most notably hypertension [4]. However, safety of PSE and phenylpropanolamine has been demonstrated in patients with controlled hypertension [21, 22]. In the present study, no hypertension was seen with either topical or systemic medication. The lack of any relevant blood pressure effects indicates that the systemic decongestant PSE was as well tolerated in this respect as the topical agent XMZ.

Aside these elements, it is worthwhile to point out the additional benefits of CTZ/PSE as compared to XMZ on the relief of nasal and ocular symptoms generally associated with PAR. These properties are likely to be associated with the anti-H1 properties of CTZ. The overall symptomatic CTZ/PSE superiority over XMZ was confirmed by the better overall self-assessment of efficacy reported through the VAS. Additionally, the amount of nasal secretions was smaller with CTZ/PSE than with XMZ.

PEF (peak expiratory flow rate) measurements, which measure the respiratory functions, were significantly greater under CTZ/PSE as compared to XMZ. This result suggests that CTZ/PSE may have a protective effect on vital capacity similar to the apparently beneficial effect on forced expiratory flow in one second (FEV1) reported with CTZ/PSE in a previous placebo-controlled study [14].

<table>
<thead>
<tr>
<th>Table 2: Adverse events.</th>
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<tr>
<td>Adverse event</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Lost power</td>
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<tr>
<td>Respiratory difficulty</td>
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<tr>
<td>Blocked nose</td>
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<tr>
<td>Bronchospasm</td>
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<tr>
<td>Conjunctivitis</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Epistaxis</td>
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<tr>
<td>Headache</td>
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<tr>
<td>PEF-reduction</td>
</tr>
<tr>
<td>PEF-reduction, bronchospasm</td>
</tr>
<tr>
<td>Uveitis</td>
</tr>
<tr>
<td>Total</td>
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</table>
XMZ and CTZ/PSE were well tolerated in this study. Fewer adverse events were reported during treatment with CTZ/PSE; these adverse events were not considered to be treatment related but due to the house dust mite challenge.

5. Conclusion
In this house dust mite nasal challenge model, rapid onset of action but short-lived effect of topical XMZ 0.1% has to be balanced against the consistent and prolonged effect of systemic CTZ/PSE combination as no significant differences between these 2 medications were noted regarding their decongestant properties. Efficacy of CTZ/PSE was already noticeable 30 min after intake. Nasal and ocular symptoms relief was more pronounced with CTZ/PSE. Fewer adverse events and a better global evaluation were also recorded for CTZ/PSE as compared to XMZ.

6. References

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