A placebo-controlled study of the nasal decongestant effect of phenylephrine and pseudoephedrine in the Vienna Challenge Chamber

Friedrich Horak, MD*†; Petra Zieglmayer, MD*; René Zieglmayer, DI†; and Patrick Lemell, PhD†; Ruji Yao, PhD‡; Heribert Staudinger, MD‡; and Melvyn Danzig, PhD‡

Background: Studies on the efficacy of phenylephrine in the treatment of nasal congestion have yielded inconsistent results, notwithstanding its approval for this indication.

Objective: To evaluate and compare the decongestant effect of a single dose of phenylephrine to placebo and pseudoephedrine in patients with seasonal allergic rhinitis.

Methods: This randomized, placebo-controlled, 3-way crossover study evaluated patient-scored nasal congestion, peak nasal inspiratory flow, and rhinomanometry at more than 6 hours in 39 grass-sensitive patients exposed to grass pollen in the Vienna Challenge Chamber. Patients were dosed with immediate-release formulations of phenylephrine, 12 mg, pseudoephedrine, 60 mg, as a control, or placebo.

Results: Phenylephrine was not significantly different from placebo in the primary end point, mean change in nasal congestion score at more than 6 hours ($P = .56$), whereas pseudoephedrine was significantly more effective than both placebo ($P < .01$) and phenylephrine ($P = .01$). Phase 1 results showed a difference between phenylephrine and placebo that was 64% of the difference between pseudoephedrine and placebo, substantially greater than the 17% difference observed for all phases. Carryover bias due to patient recall of the pseudoephedrine effect may have influenced these results. Rhinomanometry and peak nasal inspiratory flow results were consistent with these data. Neither phenylephrine nor pseudoephedrine had an effect on the nonnasal symptoms. No adverse events were reported in this study.

Conclusions: During a 6-hour observation period, a single dose of pseudoephedrine but not phenylephrine resulted in significant improvement in measures of nasal congestion. Neither phenylephrine nor pseudoephedrine had an effect on nonnasal symptoms.

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INTRODUCTION

In several recent surveys of impact and burden of allergic rhinitis, nasal congestion was consistently ranked the most bothersome symptom in both adult respondents and guardians of children with allergies.[1–3] In addition, nasal congestion was the symptom that most respondents (50% of adults and 63% of guardians of children with allergies) wanted to prevent from occurring.[3] Therapeutic options for the prevention and treatment of nasal congestion include oral decongestants (sympathomimetic agents), such as pseudoephedrine and phenylephrine, which can be administered alone or in combination with antihistamines.[4]

Many manufacturers have changed the formulation of decongestant products to include phenylephrine because of safety and tolerability concerns associated with the use of pseudoephedrine in certain patient populations and recent legislation, including the Combat Methamphetamine Epidemic Act, which requires that all products containing pseudoephedrine be kept "behind the counter."[4,5] The efficacy of phenylephrine as a substitute for pseudoephedrine has been questioned because several reports have indicated that phenylephrine does not provide consistent relief of nasal congestion or nasal resistance above that provided by placebo[5,6]; therefore, the purpose of the current study was to compare the decongestant effect of a single dose of phenylephrine to placebo and pseudoephedrine in patients with allergic rhinitis.

Allergen challenge chambers are useful in determining drug effects in allergic patients exposed to pollen in a homogeneous environment.[7] The Vienna Challenge Chamber is the longest standing allergen challenge system and has been used to determine proof-of-concept, time course, and magnitude of effect and onset of action of antihistamines, nasal corticosteroids, and similar agents.

Affiliations: * ENT University Clinic, University of Vienna, Vienna, Austria; † Allergy Center, Vienna West, Vienna, Austria; ‡ Schering-Plough Research Institute, Kenilworth, New Jersey.

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METHODS

This was a single-center, randomized, placebo-controlled, 3-way crossover study of the decongestant effect of phenylephrine compared with placebo and pseudoephedrine in patients with at least a 2-year history of symptomatic and skin test positive seasonal allergic rhinitis to grass pollen after exposure to grass pollen in the Vienna Challenge Chamber. Patients were to be treated with 1 dose of phenylephrine, 12 mg, pseudoephedrine, 60 mg, or placebo at each treatment visit with a minimum washout period of 5 days between visits. Pseudoephedrine (Sudafed Decongestant Tablets; Pfizer Consumer Healthcare, Eastleigh, Hampshire, England) and phenylephrine (Sudafed Congestion Relief Capsules; Pfizer Consumer Healthcare) were purchased locally. Placebo (blue capsules containing inactive ingredients) was supplied by Schering-Plough Research Institute. All 3 medications came packaged in individual blisters. A third party was provided a master randomization code and prepared the medication for each patient for each period by placing 1 of the appropriate blisters into a prelabeled vial. The investigator and staff did not know the identities of the medications taken; the patients knew that they took either a tablet or a capsule.

The methods for the Vienna Challenge Chamber have been previously described.[8] In brief, patients met the following minimum symptoms severity criteria during a 120-minute predose challenge in the Vienna Challenge Chamber: score of at least 2 (moderate) for nasal congestion; score of at least 6 for combined nasal symptoms (symptoms are rhinorrhea, nasal congestion, sneezing, and nasal itch); and score of at least 2 for combined nonnasal symptoms (symptoms are eye itching or burning, eye tearing, and itching of ears or palate).

The study drug was dispensed when the patient met these scores; patients remained in the Vienna Challenge Chamber for 7.5 hours. Patients were required to complete symptoms evaluations on a scale of 0, indicating none, to 3, indicating severe, at 15-minute intervals. Rhinomanometry, peak nasal inspiratory flow (PNIF), and collection of tissues used for determination of nasal secretion weights were performed at 30-minute intervals.

The primary efficacy variable was the subjective evaluation of nasal congestion expressed as an average change from baseline during the first 6.0 hours of the evaluation period. Additional efficacy end points included 2 objective measures of nasal congestion, rhinomanometry, and PNIF, which were evaluated as the average change at more than 6 hours for each of these measures. The average change at more than 6 hours also was evaluated for each of the individual nasal symptoms of rhinorrhea, sneezing, and nasal itching and nonnasal symptoms of eye itching or burning, eye tearing, and itching of the ears or palate. Safety was evaluated by recording of adverse events and measurement of vital signs.

The study was performed in accordance with applicable statutes and regulations regarding the protection of patients' rights and welfare and was approved by institutional review boards at each study site. All patients provided written informed consent before any study procedure was performed.

The primary comparison for the primary efficacy variable, subjective evaluation of nasal congestion, was phenylephrine, 12 mg, vs placebo tested at 2-sided $\alpha = .05$. Pseudoephedrine, 60 mg, was included as a positive control and was also compared with placebo. The comparison of pseudoephedrine vs placebo was performed at unadjusted $\alpha = .05$, primarily to validate the trial results. In addition, phenylephrine was compared with pseudoephedrine to evaluate relative efficacy. Pairwise comparisons were made using linear contrasts of the treatment means obtained from an analysis of variance model that extracts sources of variation due to treatment, patient, and phase. The primary comparison for all of the secondary end points was phenylephrine vs placebo tested at 2-sided $\alpha = .05$; pseudoephedrine was also compared with placebo.

RESULTS

Thirty-nine patients were randomized; 38 patients completed treatment, and 1 patient discontinued participation in the study for reasons unrelated to treatment with study drug after the first dose (pseudoephedrine). Patients were predominantly white (97%) and female (59%); age ranged from 19 to 46 years (mean, 27 years). Baseline (at the time the patients qualified) nasal congestion scores were 2.20 for phenylephrine and placebo and 2.26 for pseudoephedrine.

Phenylephrine was not significantly different from placebo in decreasing nasal congestion scores at any evaluation time. The average first 6-hour postbaseline decrease nasal congestion score was 7.1% for phenylephrine treatment compared with 2.2% for placebo treatment ($P = .56$). Comparatively, pseudoephedrine, with an average 6-hour mean percentage decrease from baseline in nasal congestion score of 21.7%, was significantly more effective than either placebo ($P < .01$) or phenylephrine ($P = .01$). The difference between phenylephrine and placebo in the average change from baseline during the first 4 hours after dosing (0.19 to 0.16 point) was similar to the difference in the average change from baseline during the first 6 hours after dosing (0.18 to 0.12 point). The time course for nasal congestion is shown in Figure 1. The first time point where pseudoephedrine was statistically different from placebo in nasal congestion was at 30 minutes; because phenylephrine did not differentiate from placebo, we could not determine its onset of action.

No significant phase effect ($P = .72$) was found in the analysis of the primary end point. In addition, no significant sequence effect ($P = .89$) was found. When data from the first phase of a crossover are evaluated, however, the results can be similar to what could be expected in a parallel-group design. For phase 1 data in this study, the difference between phenylephrine and placebo (0.31 to 0.10 point) was 64% of the difference between pseudoephedrine and placebo (0.43 to 0.10 point), which is greater than the 17% phenylephrine to pseudoephedrine ratio noted when all phases were considered.

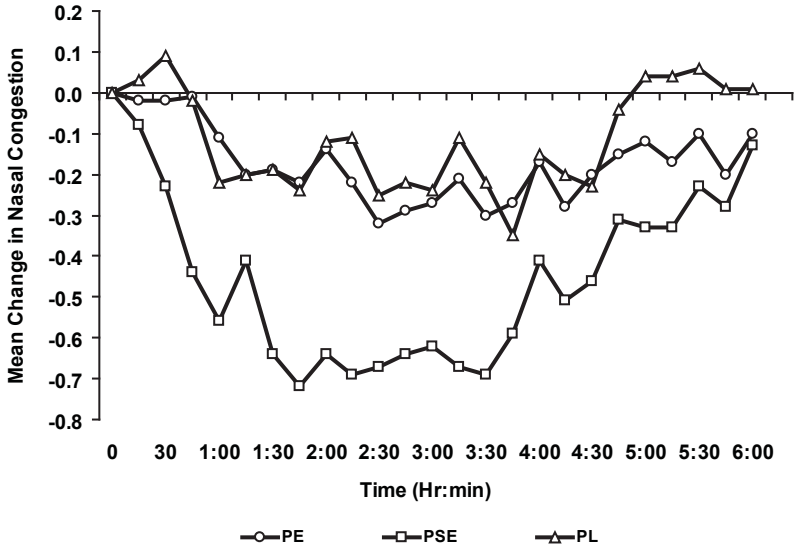

Figure 1. Mean change in subjective nasal congestion scores at each 15-minute interval after drug administration. Baseline values were 2.20 (phenylephrine [PE]), 2.26 (pseudoephedrine [PSE]), and 2.20 (placebo [PL]).

The results of rhinomanometry (Fig 2) and PNIF (Fig 3), 2 objective measures of nasal decongestant effects, were consistent with the results of the primary measurement. Phenylephrine had no significant effect on nasal airflow compared with placebo as evidenced from the rhinomanometry results ($P = .12$), whereas pseudoephedrine was significantly more effective than placebo ($P = .03$, sum of right and left nostrils, average 6 hours after dosing). When averaged for the first 6 hours of the evaluation period, PNIF showed no significant effect on nasal airflow for phenylephrine ($P = .94$) vs placebo and a borderline significant improvement for pseudoephedrine ($P = .07$) vs placebo. However, the pseudoephedrine group showed significant improvement during the first 4 hours after dosing, in line with the expected duration of action of a 60-mg dose of pseudoephedrine. At the hour 4 measurement, the pseudoephedrine group had improved significantly ($P = .01$) vs placebo, whereas the phenylephrine group had not separated from placebo ($P = .87$).

For the other individual nasal symptom scores averaged during the first 6 hours, pseudoephedrine was significantly better than placebo for rhinorrhea ($P = .04$) and sneezing ($P = .01$), whereas phenylephrine was similar to or worse

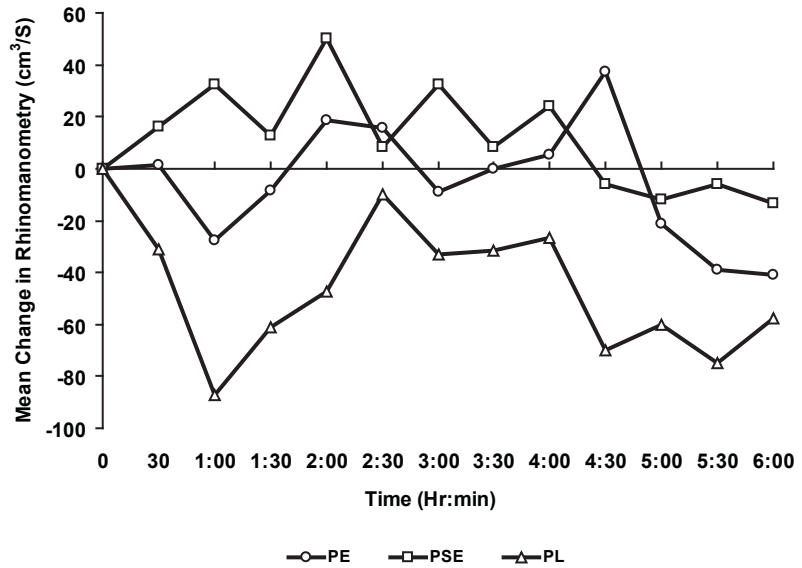

Figure 2. Mean change in rhinomanometry measurements (sum of right and left nostrils) at each 30-minute interval after drug administration. Baseline values were 366.1 (phenylephrine [PE]), 406.2 (pseudoephedrine [PSE]), and 400.9 (placebo [PL]) at 150 Pa (cm^3/s).

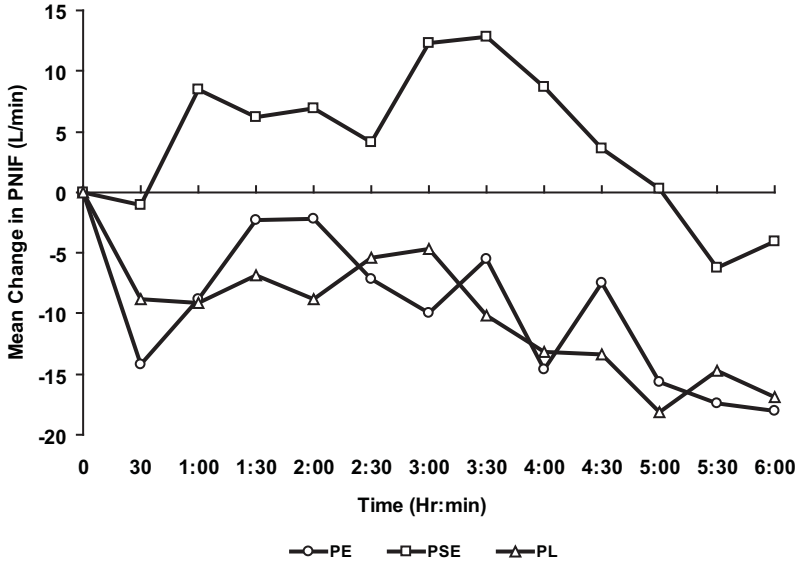

Figure 3. Mean change in peak nasal inspiratory flow (PNIF) scores at each 30-minute interval after drug administration. Baseline values were 104.6 (phenylephrine [PE]), 108.7 (pseudoephedrine [PSE]), and 107.0 (placebo [PL]) L/min.

than placebo for each (data not shown). Neither phenylephrine nor pseudoephedrine had a significant improvement compared with placebo on nasal itching or the nonnasal symptoms (eye itching or burning, eye tearing, itching of ears or palate) (data not shown). A greater decongestant effect was found compared with placebo in female patients than in male patients taking pseudoephedrine; this differential treatment response was not seen for phenylephrine.

No adverse events were reported in this single-dose study, and no treatment differences were observed in vital signs. These results indicated that the single doses of phenylephrine, 12 mg, and pseudoephedrine, 60 mg, were safe and well tolerated, although the study was not powered to find statistically significant differences in safety.

DISCUSSION

In this study, statistical significance ($P = .56$) was not observed for the primary efficacy variable, the average change from baseline during a 6-hour evaluation period in nasal congestion, in patients with seasonal allergic rhinitis treated with a single dose of phenylephrine, 12 mg, vs patients treated with placebo. Comparatively, treatment with a single dose of pseudoephedrine, 60 mg, showed significant improvement in nasal congestion compared with placebo ($P < .01$) and phenylephrine ($P = .01$). Phenylephrine showed 17% of the decongestant activity demonstrated by pseudoephedrine over placebo.

When results were evaluated by phase of the crossover, the phase 1 difference between phenylephrine and placebo was 64% of the difference between pseudoephedrine and placebo. This result is similar to what would be expected in a parallel-group design. In this crossover-design study, patients may have recalled the effect of pseudoephedrine when pseudoephedrine was taken before other treatments and influenced their symptom evaluation. The 3 sequences that had phenylephrine taken before pseudoephedrine in any phase had greater changes in the mean decongestant effects compared with placebo of phenylephrine, whereas the other 2 sequences that had phenylephrine taken after pseudoephedrine in any phase had raw mean decongestant effects that were considerably lower when compared with placebo of phenylephrine. This finding suggests that bias may have been introduced because of patient recall of the pseudoephedrine effect in a previous phase.

Changes in patients' symptom scores for nasal congestion and objective measures of nasal airflow as a result of the administration of a therapeutic agent do not always occur in parallel[9] because, unlike other symptoms of allergic rhinitis, the discomfort felt by patients with nasal congestion does not always correlate with the aspects of the symptom that a physician can evaluate, such as nasal patency.[10,11] To reduce the possibility that the current study would underestimate the efficacy of phenylephrine in the relief of nasal congestion, 2 objective measures were also used. Both PNIF and rhinomanometry were consistent with the subjective measure of efficacy in this study with no demonstrated improvement in either measure after the administration of phenylephrine, whereas a significant improvement in rhinomanometry and an increase in PNIF were seen with pseudoephedrine treatment.

As noted, pseudoephedrine provided a significant improvement over placebo for rhinorrhea and sneezing but not nasal itching or the nonnasal symptoms. Similar reductions in other rhinitis symptoms after treatment with pseudoephedrine have been noted,[12] although it is generally thought that the oral decongestants have no effect on other symptoms because

there is no direct effect of decongestants on allergic mediators.[4] It has been suggested that the relief of symptoms other than nasal congestion by decongestant agents may reflect a "halo effect" because a reduction in nasal congestion may lead to an overall improvement in the patient's sense of well-being and reduced perception of the severity of other rhinitis symptoms.[12]

Although patients were exposed for 7.5 hours after dosing, the primary end point was the average for the first 6 hours. This approach was in keeping with the dosing regimens of the short-acting form of phenylephrine (every 6 hours) and pseudoephedrine (every 4 to 6 hours) that were used in this study. Although the dosing regimen for these decongestants is similar, the half-life of phenylephrine is shorter than that of pseudoephedrine,[10,13] so it may be possible that a significant effect of phenylephrine occurred during the initial response to the treatment. To determine if phenylephrine treatment resulted in significant improvements in either the subjective or objective measures of nasal congestion, the 4-hour time point was also examined, showing similar results. This finding suggests that it is unlikely that the lack of efficacy with phenylephrine was a result of using the short-acting formulation.

Both pseudoephedrine and phenylephrine have been described as safe and effective drugs.[14] A recent letter questioned the effectiveness of phenylephrine as a nasal decongestant when given orally.[6] Our study was clinically complete when this letter appeared online in May 2006. Within the limitations of the first phase data from this small chamber study, it appears that phenylephrine may have activity, although the magnitude and the duration of effect may not be optimized by the current existing doses and formulations. However, because no difference between phenylephrine and placebo for any of the primary subjective or objective measures of nasal congestion was found at any time point, this would suggest that there is little, if any, appreciable effect of phenylephrine compared with placebo in the relief of nasal congestion. The results of the current study are similar to the results of a recent meta-analysis that examined the efficacy and safety of phenylephrine in relieving nasal congestion that occurred because of a variety of causes (eg, "head cold," chronic sinusitis, allergies).[5] In that study, the decongestive effects of phenylephrine also were not consistently any better than placebo.[5]

The following conclusions can be drawn from this study. First, in this crossover design, patients with seasonal allergic rhinitis treated with a single dose of 12 mg of phenylephrine were not significantly different from placebo-treated patients in reduction of their nasal congestion scores from baseline; pseudoephedrine at a dose of 60 mg was superior to placebo. It is possible that recall bias in the crossover design may have influenced this result. Second, treatment with a single dose of phenylephrine, 12 mg, and pseudoephedrine, 60 mg, in male and female patients with seasonal allergic rhinitis, ages 19 to 46 years, was safe and well tolerated.

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Requests for reprints should be addressed to:
Melvyn R. Danzig, PhD
2015 Galloping Hill Rd
Kenilworth, NJ 07033
E-mail: Melvyn.danzig@spcorp.com