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

Friedrich Horak, MD*†; Petra Ziegelmayer, MD*; René Ziegelmayer, 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.


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.

Funding Sources: This study was supported by a grant from Schering-Plough Research Institute.

Disclosures: Drs Danzig, Yao, and Staudinger are employees of Schering-Plough Research Institute.

Trial Registration: clinicaltrials.gov Identifier: NCT00276016

Received for publication August 19, 2008; Received in revised form November 11, 2008; Accepted for publication November 30, 2008.
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 medications. 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. In brief, patients met the following criteria: 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 medications. 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. In brief, patients met the following criteria: 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.

The primary efficacy variable was the subjective evaluation of nasal congestion, was phenylephrine, 12 mg, vs placebo tested at 2-sided α = .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 α = .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 α = .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.
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 \((P = .03, \text{sum of right and left nostrils, average 6 hours after dosing})\). 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
than placebo for each (data not shown). Neither phenyleph-
rine 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 statis-
tically significant differences in safety.

DISCUSSION
In this study, statistical significance \( (P = .56) \) was not ob-
served 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 im-
provement in nasal congestion compared with placebo \( (P <
.01) \) and phenylephrine \( (P = .01) \). Phenylephrine showed
17% of the decongestant activity demonstrated by pseudo-
ephedrine 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 pseudo-
ephedrine was taken before other treatments and influenced
their symptom evaluation. The 3 sequences that had phenyl-
ephrine 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 consid-
erably 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 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 rhinoma-
ometry were consistent with the subjective measure of effi-
cacy 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 treat-
ment.

As noted, pseudoephedrine provided a significant improve-
ment 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. 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.

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 regimen 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, 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. A recent letter questioned the effectiveness of phenylephrine as a nasal decongestant when given orally. 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 suggests 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). In that study, the decongestive effects of phenylephrine also were not consistently any better than placebo.

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.

ACKNOWLEDGMENTS
We thank Sandria De Sapio and Karin Gansch for study monitoring; Lucy Shneyer, MS, for statistical oversight; and Craig Ostroff, PharmD, for logistical and regulatory support.

REFERENCES

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

120 ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY