

Oral Phenylephrine HCl for Nasal Congestion in Seasonal Allergic Rhinitis: A Randomized, Open-label, Placebo-controlled Study

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What is already known about this topic? The efficacy of phenylephrine for the treatment of nasal congestion has been questioned. The US Food and Drug Administration has requested that large, well-constructed, dose-ranging trials be conducted.

What does this article add to our knowledge? Phenylephrine hydrochloride doses of up to 40 mg every 4 hours are not significantly better than placebo in reducing subjective nasal congestion scores in individuals suffering from seasonal allergic rhinitis.

How does this study impact current management guidelines? These findings are of medical and scientific importance for consumers and health care professionals to guide their recommendations for nasal congestion products.

BACKGROUND: Phenylephrine hydrochloride (PE HCl) is widely used for the treatment of nasal congestion, but efficacy at the 10-mg dose is not known for certain. The Food and Drug Administration has requested that sufficiently powered, multicenter, dose-ranging studies be conducted to assess the efficacy and safety of PE HCl.

OBJECTIVE: To evaluate subjective nasal congestion symptom relief and safety of 4 different doses of PE HCl immediate-release 10-mg tablets and placebo in adults with seasonal allergic rhinitis (SAR).

METHODS: This multicenter, phase 2, parallel, open-label trial randomized 539 adults with SAR (but otherwise healthy) to 7 days of treatment with either PE HCl 10-mg tablets at fixed

doses of 10, 20, 30, or 40 mg or placebo. The primary efficacy end point was the mean change from baseline over the entire treatment period in daily reflective nasal congestion score. Other efficacy end points and safety were also evaluated.

RESULTS: None of the PE HCl treatment groups had a statistically significant change from baseline in instantaneous or reflective nasal congestion scores compared with the placebo group. PE HCl was well tolerated at doses of up to 30 mg. At least 1 treatment-emergent adverse event was experienced by 18.4% of the participants, the most common being headache (3.0%).

CONCLUSIONS: PE HCl, at doses of up to 40 mg every 4 hours, is not significantly better than placebo at relieving nasal congestion in adults with SAR. The phenylephrine section of the Food and Drug Administration monograph on over-the-counter cold, cough, allergy, bronchodilator, and antiasthmatic products should be revised accordingly. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:702-8)

Key words: Seasonal allergic rhinitis; Phenylephrine HCl; Nasal congestion; Dose-ranging trial; Oral decongestant

Nasal symptoms attributed to seasonal or perennial allergic rhinitis (AR) are highly prevalent in the United States, occurring in 11.9% to 30.2% of the adolescent and adult population.¹ The impact on sufferers and society is substantial, with symptoms of AR adversely affecting sleep and quality of life,² and leading to losses in mean total productivity, including absenteeism and lost productivity at work.³ Furthermore, AR is associated with a high rate of comorbidities such as allergic conjunctivitis, sinus disease, and asthma.⁴ Of the cardinal nasal symptoms of AR (itch, sneeze, rhinorrhea, nasal congestion), nasal congestion occurs most often (in 85% of AR sufferers) and is considered by those with AR to be more bothersome than the other symptoms.⁵

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Abbreviations used

<i>AE</i> -adverse event
<i>AR</i> -allergic rhinitis
<i>BP</i> -blood pressure
<i>EE</i> -efficacy evaluable
<i>FDA</i> -Food and Drug Administration
<i>HR</i> -heart rate
<i>ITT</i> -intent-to-treat
<i>MAO</i> -monoamine oxidase
<i>OTC</i> -over the counter
<i>PDE</i> -pseudoephedrine
<i>PE HCl</i> -phenylephrine hydrochloride
<i>SAR</i> -seasonal allergic rhinitis
<i>SBP</i> -systolic blood pressure
<i>TEAE</i> -treatment-emergent adverse event

Many treatments, including oral decongestants, first- and second-generation antihistamines,^{6,7} intranasal corticosteroids,⁸ mast cell stabilizers,⁹ leukotriene modifiers such as montelukast,^{10,11} and intranasal decongestants,^{4,12} are available over the counter (OTC) or by prescription to alleviate the nasal congestion associated with AR. Clinical trial results show varying degrees of efficacy and tolerability, and use of some products is limited by undesirable and possibly serious adverse effects such as sedation and performance impairment (with first-generation antihistamines)⁶ or rhinitis medicamentosa (associated with intranasal decongestants).^{4,12}

Oral decongestants such as pseudoephedrine (PDE) and phenylpropanolamine are effective decongestants,¹³ although the Food and Drug Administration (FDA) removed phenylpropanolamine from OTC sale in 2005 because of increased risk of hemorrhagic stroke.^{14,15} Accessibility to PDE has been limited in the United States since 2006 with the adoption of legislation calling for a comprehensive system of controls regarding the distribution and sale of drug products potentially used in the illicit production of methamphetamine.¹⁶⁻¹⁸ Phenylephrine hydrochloride (PE HCl 10 mg) tablets, another oral decongestant, are marketed for OTC use in the United States for temporary relief from nasal congestion due to the common cold, hay fever, or other upper respiratory tract allergies, and for temporary relief from sinus congestion and pressure. However, the efficacy of PE HCl 10-mg tablets—the recommended oral dose for adults and children (≥ 12 years) for relief from nasal congestion—has been questioned.^{16,18,19} A systematic review and meta-analysis of many of the studies that supported the original 1976 FDA labeling for nonprescription use of PE did not find that PE HCl 10 mg is effective in the treatment of nasal congestion.²⁰ A study showed that patients with seasonal allergic rhinitis (SAR) who were exposed to grass pollen in an environmental exposure unit and treated with a single dose of 12-mg PE HCl did not show a significant change from baseline in nasal congestion during a 6-hour evaluation period compared with patients treated with placebo in contrast to PDE 60 mg.²¹ There was no statistically significant difference between PE HCl 10 mg and placebo in relieving nasal congestion in a second environmental exposure unit study in contrast to a combination of loratadine-montelukast.²²

The FDA convened a Nonprescription Drugs Advisory Committee on December 14, 2007, in response to a citizen petition (Docket No. 2007P-0047/CP1) filed with the FDA in early 2007 arguing that available data do not support the efficacy of the 10-mg dose of PE HCl for adults. The committee

concluded by a vote of 9 to 3 that “Additional studies are needed to assess the efficacy and safety of higher doses (eg, 25 mg).”¹⁹ The lowest effective dose of PE HCl without clinically significant cardiovascular effects is not known, and the efficacy of doses higher than the 10-mg oral dose every 4 hours has not been studied in adequately powered dose-response studies.¹⁶ Consequently, the present study was designed to evaluate symptom relief of nasal congestion with the approved 10-mg dose of PE HCl, as well as 3 higher doses (20, 30, and 40 mg) taken for 7 days, versus placebo in individuals with nasal congestion associated with SAR. The maximum dose selected was based on previous phase 1 safety trials that found it to have no significant effect on systolic blood pressure (SBP) or heart rate (HR; MSD Consumer Care, Inc, data on file). A parallel, 5-arm, placebo-controlled design using subjective symptom measures was chosen to comply with the FDA’s Draft Guidance for Industry for a dose-ranging study in healthy atopic patients with SAR.²³

METHODS

Participants

Healthy participants older than 18 years were included if they had a documented or patient-reported (1) history of SAR caused by spring pollen within the last 4 years and (2) symptoms over at least the last 2 spring allergy seasons. Other key inclusion criteria included documented positive responses on skin test or *in vitro* test within the last 4 years for specific IgE, such as a radioallergosorbent or paper radioimmunosorbent test to spring pollen allergens present and prevalent in the participant’s geographic region. After an allergy medicine washout period, participants needed to have continued symptoms of nasal congestion while otherwise healthy. Key exclusion criteria included a history or presence of hypertension; persistent asthma, rhinitis medicamentosa, or acute or chronic sinusitis; initiation of allergen immunotherapy within a month preceding enrollment; or use of corticosteroids in the last 30 days.

Study design and treatment

This was a multicenter, randomized, phase 2, parallel, 5-arm, open-label, placebo-controlled, dose-ranging trial of treatment for 7 days (protocol #CL 2010-06; NCT01330017). Screening (visit 1, day –30 to day –5) recorded demographic and other information; baseline was the diary run-in from day –4 to day –1 during which participants did not take any medication with the exception of daily loratadine; day 1 to day 7 (collectively visit 2) was the treatment phase during which they received the randomized medication and continued to take daily loratadine; day 8 (visit 3), posttreatment, recorded nasal congestion scores and adverse events (AEs) as was done for visit 2; day 22 to day 28 (visit 4) comprised telephone follow-up reviews to record AEs.

The study was performed after institutional review board approval and was designed, implemented, and reported in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and ethical principles laid down in the Declaration of Helsinki for experiments involving humans. Participants provided written, institutional review board–approved informed consent. The study sites and 34 investigators—in private practices—were located throughout the United States.

A validated program for the treatment sequence list and randomization code was used to randomize eligible participants into 1 of 5 treatment groups: PE HCl 10-mg immediate-release tablets at fixed doses of 10, 20, 30, or 40 mg, or placebo. Commercial PE

10-mg tablets were used. Both PE 10-mg and placebo tablets were red and concave, but not exactly matching.

Treatment for nasal congestion was to be taken orally every 4 hours, with no more than 6 doses in 24 hours. *Adherence* was defined as administration of at least 4 of the 6 doses per 24-hour period. Participants received background treatment with loratadine 10 mg for 4 to 7 days during the run-in phase and then for 7 days beginning at visit 2 until visit 3. Loratadine was used to avoid participants' responses to nasal congestion symptoms being influenced by the background of other SAR symptoms based on previous published trials,^{24,25} and could have prevented dropouts.

Outcome measures

Efficacy. The primary end point was mean change from baseline over the entire treatment period (ie, 7 days) in daily reflective nasal congestion score, obtained from participants' diaries and defined as the average of the morning and evening reflective nasal congestion score for the entire treatment period. Participants rated the severity of congestion symptoms on a 4-point scale from 0 (none) to 3 (severe). Reflective assessment (ie, self-evaluation of symptom severity over the preceding 12 hours) was recorded just before the 8:00 AM dose and approximately 12 hours later just before the 8:00 PM dose. Instantaneous assessment is self-evaluation of symptom severity at the moment of assessment before the next dose. *Baseline* was defined as the average of the daily scores (including the morning assessment on the day of randomization) over 4 consecutive 24-hour periods before randomization. The maximum duration in the clinical trial for a given participant was approximately 8 weeks, including the screening and follow-up evaluations.

Secondary end points were the mean changes from baseline in (1) AM and PM symptom scores (calculated and analyzed separately) for the reflective symptom assessment; (2) instantaneous symptom assessment scores over the entire treatment period; (3) reflective symptom assessment score for each day during the treatment period to assess onset of action and durability of the response; (4) instantaneous symptom assessment score for each day during the treatment period to assess onset of action and durability of the response; and *time to maximal effect*, defined as the earliest time the nasal congestion symptom score demonstrated the greatest numerical difference from placebo in change from baseline. Baseline for instantaneous symptom assessment score was the day 1 predose assessment.

Safety. Safety end points were AEs, treatment-emergent adverse events (TEAEs), serious AEs, vital signs, physical examination, and 12-lead electrocardiograms. Electrocardiograms were measured at screening and day 8.

Statistical analysis

This trial was designed to have a power of 94% to detect a difference of at least 1 unit between PE and placebo with respect to the change from baseline in the nasal congestion symptom score on day 8. This required 100 participants per treatment group using a 2-sided test with 5% significance level assuming an SD of 2.0 units.

The intent-to-treat (ITT) population was used for efficacy analyses and included all participants who were randomized to a study treatment; the safety population included all participants who received at least 1 dose of study medication; the efficacy evaluable (EE) population included all participants in the ITT population who had at least 1 full-day (morning and evening) of nonmissing post-dose reflective nasal congestion symptom scores.

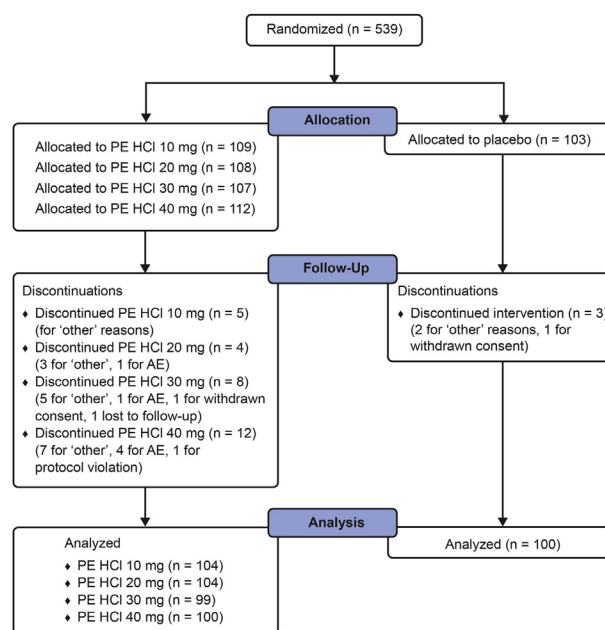


FIGURE 1. Disposition of participants. The ITT population included all participants who were randomized to a study treatment. The safety population included all participants who took at least 1 dose of study medication. The EE population (ie, those analyzed) included all participants in the ITT population who had at least 1 complete full day (morning and evening) of postdose reflective nasal congestion symptom scores.

An analysis of covariance model was used for analysis of the mean change from baseline versus placebo for all end points, with adjustments for the baseline score, investigative site, age, and sex. Multiple comparisons between each of the 4 active doses and placebo for the primary efficacy end point were performed as a closed family of tests, each at the .05 level of significance, and proceeded in sequence from the highest dose to the lowest dose to control the overall significance level of .05. Secondary efficacy end points were analyzed as for the primary efficacy end point, but not adjusted for multiplicity. For each participant, daily scores were averaged over all nonmissing days and used to calculate the mean values over the treatment interval to evaluate the effectiveness of PE over the entire treatment period.

Summaries of safety data were descriptive and based on the treatment actually received. SAS Version 9.2 (SAS Institute, Inc, Cary, NC) was used for all analyses.

RESULTS

Participants' characteristics

A total of 539 participants were randomized (Figure 1), 109 to PE HCl 10 mg, 108 to PE HCl 20 mg, 107 to PE HCl 30 mg, 112 to PE HCl 40 mg, and 103 to placebo. All participants in the ITT population received the treatment to which they were randomized. A total of 517 of 539 (95.9%) participants were in the EE population. All 539 participants were analyzed for safety. Table I presents baseline demographic characteristics and clinical characteristics. The first participant enrolled on March 30, 2011, and the last completed the study on June 6, 2011.

Overall, 32 of 539 (5.9%) participants discontinued the study early. Reasons included AEs (6 of 539; 1.1%), withdrawn consent (2 of 539; 0.4%), lost to follow-up (1 of 539; 0.2%),

TABLE 1. Demographic characteristics and baseline characteristics by treatment—the safety population

Characteristic	Phenylephrine HCl				Placebo (N = 103)	Overall (N = 539)
	10 mg (N = 109)	20 mg (N = 108)	30 mg (N = 107)	40 mg (N = 112)		
Sex n (%)						
Male	33 (30.3)	45 (41.7)	34 (31.8)	60 (53.6)	42 (40.8)	214 (39.7)
Female	76 (69.7)	63 (58.3)	73 (68.2)	52 (46.4)	61 (59.2)	325 (60.3)
Race, n (%)						
White	81 (74.3)	85 (78.7)	85 (79.4)	93 (83.0)	78 (75.7)	422 (78.3)
Black/African American	24 (22.0)	20 (18.5)	15 (14.0)	15 (13.4)	22 (21.4)	96 (17.8)
Asian	3 (2.8)	3 (2.8)	4 (3.7)	4 (3.6)	2 (1.9)	16 (3.0)
American Indian/Alaskan Native	0	0	1 (0.9)	0	1 (1.0)	2 (0.4)
Native Hawaiian/Pacific islander	1 (0.9)	0	2 (1.9)	0	0	3 (0.6)
Ethnicity, n (%)						
Hispanic/Latino	16 (14.7)	28 (25.9)	14 (13.1)	19 (17.0)	15 (14.6)	92 (17.1)
Non-Hispanic/Latino	93 (85.3)	80 (74.1)	93.0 (86.9)	93 (83.0)	88 (85.4)	447 (82.9)
Age (y)						
Mean ± SD	39.3 ± 11.25	36.8 ± 11.08	38.9 ± 12.65	39.6 ± 13.10	38.9 ± 11.96	38.7 ± 12.04
Median	40.0	37.0	41.0	38.5	39.0	39.0
Min, Max	18.0, 61.0	18.0, 63.0	18.0, 72.0	19.0, 77.0	18.0, 67.0	18.0, 77.0
Height (cm)						
Mean ± SD	168.6 ± 11.16	170.3 ± 10.4	167.9 ± 9.31	170.6 ± 9.92	169.7 ± 9.24	169.4 ± 10.06
Median	168.0	170.0	168.0	171.0	168.0	169.0
Min, Max	126.0, 206.0	152.0, 203.0	145.0, 190.0	131.0, 193.0	149.0, 194.0	126.0, 206.0
Weight (kg)						
Mean ± SD	79.9 ± 17.28	81.2 ± 17.34	77.3 ± 17.48	81.7 ± 19.03	79.5 ± 20.61	80.0 ± 18.38
Median	78.9	79.5	75.0	78.1	77.4	77.3
Min, Max	50.4, 125.0	54.0, 136.0	46.7, 126.4	51.8, 157.5	50.5, 149.9	46.7, 157.5
Body mass index (kg/m ²)						
Mean ± SD	28.2 ± 5.85	27.9 ± 5.12	27.4 ± 5.56	28.1 ± 6.44	27.5 ± 6.24	27.8 ± 5.85
Median	27.1	27.4	26.0	27.2	26.5	26.8
Min, Max	18.0, 50.5	18.9, 44.4	17.2, 47.6	17.3, 55.8	18.4, 47.1	17.2, 55.8

protocol violation (1 of 539; 0.2%), and other (22 of 539; 4.1%).

Major protocol deviations occurred in 15 of 539 (2.8%) participants, including 5 (0.9%) who did not meet inclusion criteria, 4 (0.7%) who did not follow procedures, 3 (0.6%) who received an incorrect dosing, 2 (0.4%) who did not meet blood pressure (BP) criteria, 1 (0.2%) who was noncompliant, and 1 (0.2%) who was not discontinued according to protocol requirements. The mean ± SD study medication adherence (%) was 79.9 ± 18.0, 80.5 ± 15.1, 78.9 ± 19.1, 77.3 ± 19.9, and 83.7 ± 15.3 for the 10-, 20-, 30-, and 40-mg and placebo groups, respectively, for both the ITT and safety populations. Mean ± SD daily dose of PE HCl (mg/day) actually taken according to participants' diaries was 44.5 ± 10.3, 90.4 ± 16.2, 131.5 ± 30.9, and 171.9 ± 43.7, respectively. The mean ± SD number of days exposure to loratadine was 6.7 ± 1.3, 6.8 ± 1.1, 6.8 ± 1.1, 6.4 ± 1.7, and 6.9 ± 0.7, respectively.

Efficacy

For the primary end point, none of the active treatment groups (ITT and EE populations) had a statistically significant change from baseline in reflective nasal congestion scores compared with placebo. The mean ± SD change from baseline in reflective nasal congestion scores (ITT population) was -0.460 ± 0.537 , -0.499 ± 0.504 , -0.508 ± 0.562 , -0.461 ± 0.531 , and $-0.428 \pm$

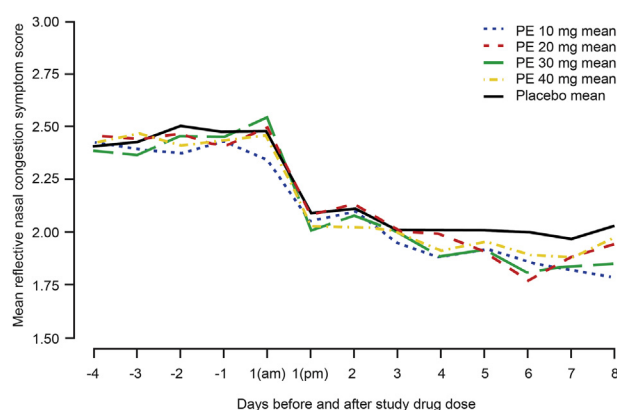


FIGURE 2. Reflective nasal congestion scores by treatment and study day (ITT population). Because the y-axis does not begin from 0, the figure may exaggerate the placebo effect of the first dose.

0.553 for the PE HCl 10-, 20-, 30-, and 40-mg and placebo groups, respectively (Figure 2).

All secondary end point comparisons were not statistically significant, except for some on day 6 favoring PE, such as the change from baseline for the evening reflective nasal congestion scores ($P = .0188$), the response rate ($P = .031$), and the change

TABLE II. Summary of common (>2%) TEAEs by system organ class, preferred term, and treatment—the safety population

System organ class/preferred term*	PE HCl 10 mg (N = 109)	PE HCl 20 mg (N = 108)	PE HCl 30 mg (N = 107)	PE HCl 40 mg (N = 112)	Placebo (N = 103)	Overall (N = 539)
Nervous system disorders, n (%)	8 (7.3)	10 (9.3)	6 (5.6)	4 (3.6)	2 (1.9)	30 (5.6)
Headache	6 (5.5)	4 (3.7)	3 (2.8)	3 (2.7)	0	16 (3.0)
Gastrointestinal disorders, n (%)	3 (2.8)	4 (3.7)	2 (1.9)	9 (8.0)	2 (1.9)	20 (3.7)
Dry mouth	0	0	0	3 (2.7)	1 (1.0)	4 (0.7)
Nausea	1 (0.9)	1 (0.9)	1 (0.9)	4 (3.6)	0	7 (1.3)

*System organ classes and preferred terms are coded using MedDRA version 13.1. A participant with multiple occurrences of an AE is counted only once in the system organ class and preferred term category. Greater than 2% cutoff applied to preferred terms within any treatment.

from baseline for the daily reflective nasal congestion scores ($P = .0201$), all for the 20-mg PE HCl group compared with placebo. The mean change from baseline for the instantaneous symptom assessment score was not significantly different from placebo on any day for any active treatment group.

The response rate generally increased over time in all treatment groups, including placebo. The time to maximal effect was 5.5 days for all PE treatment groups (ITT and EE populations).

Safety

At least 1 TEAE was experienced by 99 of the 539 (18.4%) participants (Table II), the most common being headache (16 of 539; 3.0%). A participant in the PE HCl 40-mg group reported serious AEs of chest and lower jaw pain during the study that resolved after PE withdrawal. Five additional participants reported nonserious TEAEs that led to study drug withdrawal, 3 of whom were in the PE HCl 40-mg group. The 5 nonserious TEAEs were lethargy, a case each of mild and moderate elevated BP probably related to PE, possible sinus infection, and a mild asthma flare. No clinically significant changes were observed in PR, QRS, QT, or QT_c interval or mean ventricular rate for any treatment group. One participant (on PE HCl 10 mg) had a clinically significant change in electrocardiogram (first-degree atrioventricular block) posttreatment. Dose-related increases were observed in seated office SBP and dose-related decreases in seated office HR on day 1; events resolved by day 8. No dose-related changes were observed in diastolic BP or temperature. No deaths were reported during the study.

DISCUSSION

There have been no large-scale, well-conducted, peer-reviewed clinical studies published supporting the effectiveness of PE for relief from nasal congestion. Despite widespread use and an FDA indication of 10 mg every 4 hours for temporary relief from nasal congestion, the most effective dose and duration of action for this indication are unknown. The present study was well designed and complied with FDA's Draft Guidance on clinical development programs for drug products for AR.²³ However, we failed to identify a dose for PE HCl in the range of 10 to 40 mg that was significantly more effective than placebo in relieving nasal congestion associated with SAR.

Previous analyses of the effectiveness of oral PE HCl as a decongestant have shown conflicting results. A meta-analysis of 7 crossover studies and a reanalysis of a parallel-group study conducted by Kollar et al¹⁷ supported the effectiveness of a single oral dose of PE 10 mg as a decongestant in adults with acute nasal congestion associated with the common cold; these findings led to the FDA review panel's conclusion that PE is effective for nonprescription relief of nasal congestion caused by the common

cold, AR, and sinusitis. However, this analysis included only 8 studies in the original 1976 FDA monograph on OTC cold, cough, allergy, bronchodilator, and antiasthmatic products, excluding 7 studies that were also included in the 1976 monograph. None of the included studies involved more than 25 patients per group, and all used nasal airway resistance as the efficacy outcome, examined to only a maximum of 240 minutes after dosing.¹⁷ Most of the studies included in a different meta-analysis by Hatton et al²⁰ were also crossover trials conducted for the purpose of FDA approval. However, this meta-analysis concluded that insufficient evidence exists that oral PE HCl is effective for nonprescription use as a decongestant at the 10-mg dose.

In light of these findings, an optimal dose of PE that is safe and produces clinically significant decongestion is still unknown. Doses of up to 30-mg PE HCl were well tolerated in the present study. However, there were dose-related increases in SBP and dose-related decreases in HR on day 1 of treatment, all of which resolved by day 8. Because oral PE HCl is systemically distributed and stimulates alpha-1 adrenergic receptors in the nasal mucosa as well as in peripheral blood vessels in a concentration-dependent manner,²⁶ it is plausible to consider cardiovascular effects due to PE HCl oral administration as a surrogate marker of decongestant efficacy. A 250-mg oral dose of PE HCl has been shown to be needed for substantial effects on HR (ie, decline of 15–35 beats/min) and BP (ie, SBP and diastolic BP increases of 15–40 and 10–30 mm Hg, respectively).²⁷ PE undergoes first-pass metabolism in the intestinal walls²⁸ and is a substrate for monoamine oxidase (MAO).²⁹ MAO inhibitors affect the metabolism of PE, resulting in greater absorption on coadministration, which can cause a dangerous rise in BP.²⁹ Appreciable cardiovascular effects have not been shown for doses less than 50 mg in patients not taking MAO inhibitors.²⁰ Attempts to produce clinically significant effects on decongestion by increasing PE doses should thus be tempered by the risks involved, particularly in patients with low first-pass metabolism of PE, such as those taking MAO inhibitors.

The lack of efficacy of oral PE HCl is hypothetically attributable to the extremely low concentration of the active moiety in plasma (in contrast to the concentration of topical PE on the nasal mucosa). The active moiety of PE is the parent (not conjugated/metabolized) molecule, exposure to which is orders of magnitude less than total PE (Schering-Plough Healthcare Products, data on file). Bioavailability of PE has been reported as being only 38%.²⁸ This bioavailability may not account for the lack of efficacy because effective drugs can have low bioavailability, such as an oral aqueous solution of morphine with a bioavailability of around 24%.³⁰ The amount of drug that reaches the appropriate receptor sites and the affinity of the drug for those receptors also matters. However, because the threshold

dose for PE HCl required to cause a decline in pulse rate and, usually, a slight increase in BP was reported as 50 mg, and because the intravenous dose needed for these effects was approximately 1/313 the dose of the oral dose,²⁷ this indicates that the lack of efficacy of PE is not because of lack of affinity for the alpha-1 adrenergic receptor. The bioavailability data in the literature (some from studies more than 30 years old), report total PE, whereas the actual bioavailability of the active parent PE is 100 times lower than that of total PE (Schering-Plough Healthcare Products, data on file). Oral doses of 10 to 40 mg of PE HCl would theoretically result in very low plasma concentrations and a short-lived time course of parent PE and therefore have minimal clinical and pressor effects, consistent with the results of the present trial. The fact that parent PE peaks within 30 minutes and decays rapidly compared with total PE, which has a much broader profile (Schering-Plough Healthcare Products, data on file), could explain some of the transient efficacy observed with PE HCl in the studies that supported the inclusion of PE in FDA's OTC Monograph for Nasal Decongestant Drug Products. These studies, most of which were conducted more than 45 years ago with small numbers of subjects, examined changes in nasal airway resistance only to a maximum of 240 minutes.^{17,20} In contrast, the present study examined subjective nasal congestion responses over 7 days of treatment and is thus likely to represent a more externally and ecologically valid measure of PE's effectiveness.

This study has its limitations. Because the tablets were similar but not identical in appearance, the study was open label. Nonetheless, because participants and trial personnel did not know the treatments administered, effectively this could be considered a double-blind study. Efficacy outcome measures relied on diary entries and not objective measures of nasal airway resistance; although an accepted method, participant recall and interpretation could be subject to bias. As a strength, use of participants' self-rated instantaneous and reflective symptom scores was in compliance with FDA guidance.²³ The study did not use a positive control, such as PDE. However, its intent was not to show that PE is significantly more effective than another approved decongestant. Loratadine was administered as a study drug to prevent dropouts and the confounding effects of AR symptoms on the perception of congestion relief. Loratadine is not effective for congestion relief.^{24,25}

Although the study was conducted solely in individuals with SAR, results could conceivably generalize to individuals with nasal congestion from other causes, such as the common cold or sinusitis.

In conclusion, despite the common current use of PE, this study's results document its lack of efficacy at doses from 10 to 40 mg every 4 hours. In addition, there are some associated AEs at these doses. Therefore, the PE section of the FDA monograph on OTC cold, cough, allergy, bronchodilator, and antiasthmatic products should be revised accordingly.

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