Original Article

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

Eli O. Meltzer, MD[a], Paul H. Ratner, MD, MBA[b], and Thomas McGraw, PhD[c] *San Diego, Calif; San Antonio, Texas; and Kenilworth, NJ*

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. **(J Allergy Clin Immunol Pract 2015;■:■-■)**

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]

[a]Allergy & Asthma Medical Group & Research Center, San Diego, Calif
[b]Sylvana Research, San Antonio, Texas
[c]Merck & Co, Inc, Kenilworth, NJ

Financial support for the conduct of research and the preparation of this article was provided by Merck (NCT01330017). The sponsor was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflicts of interest: E. O. Meltzer has received research support from Merck, Alcon Amgen, Apotex, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline (GSK), HRA, Kalypsys, Novartis, OnoProctor & Gamble, Rigel, Shionogi, Sunovion, and Teva; has received lecture fees from Alcon, Meda, Merck, Mylan, Sunovion, and Teva; and has received consultancy fees from Alcon, Alexza, AstraZeneca, Bausch + Lomb, Boehringer Ingelheim, Forest, Johnson & Johnson, Kalypsys, Meda, Merck, Mylan, Proctor & Gamble, Rigel, Sanofi, Sunovion, and Teva. P. H. Ratner has received research support from Merck, GSK, Amphastar, Teva, Novartis, and Apotex. T. McGraw was a former employee of Merck.

Received for publication February 10, 2015; revised April 29, 2015; accepted for publication May 7, 2015.

Available online ■■

Corresponding author: Thomas McGraw, PhD, PO Box 231, Millington, NJ 07946. E-mail: thomas_p_mcgraw@yahoo.com.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.05.007

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