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SCIENTIFIC INVESTIGATIONS

Treatment of Severe Snoring With a Combination of Pseudoephedrine Sulfate and Domperidone

Augusto Larrain, M.D., F.A.C.S.[1,2]; Monica Hudson, R.N.[1]; Jason A. Dominitz, M.D., M.H.S.[3]; Charles E. Pope II, M.D.[3]

[1]Clinica Servet, Santiago, Chile; [2]Clinica Central, Santiago, Chile; [3]University of Washington, Seattle, WA

Study Objectives: Pharmacologic treatment of severe snoring has not been considered to be of great value. The objective of this study was to determine whether the combination of a nasal decongestant and a prokinetic drug would decrease or eliminate severe snoring.

Methods: Thirty healthy individuals whose sleeping partners reported that the patients had severe nightly snoring entered an open-label trial of 60 mg of pseudoephedrine and 10 mg of domperidone at bedtime for 30 days. Each night's snoring was scored on a diary by the sleeping partner. At the end of the open-label trial, a subset of subjects whose snoring had recurred were randomized to one or both placebo-controlled trials, either 60 mg of pseudoephedrine sulfate plus 10 mg of domperidone or to 30 mg of pseudoephedrine sulfate plus 10 mg of domperidone. In another placebo-controlled trial, the drug combination was compared with each component.

Results: In the open-label trial, 493 of 772 evaluable subject-nights were free of snoring; another 232 nights were scored as mild snoring. In the placebo-controlled trials, low-dose therapy caused a reduction in snoring, and high-dose therapy even a greater reduction in snoring. The drug combination was more effective than either agent alone.

Conclusion: Treatment with a prokinetic agent plus a nasal decongestant reduced or eliminated severe snoring in the majority of subjects treated.

Keywords: Snoring, sleep-disordered breathing, gastroesophageal reflux, nasal decongestants, prokinetic agents

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Sleep-disordered breathing of the obstructive type can range from simple snoring to obstructive sleep apnea. A Medline search using the descriptors snoring and treatment lists approximately 2500 communications. Almost all forms of therapy rely on mechanical alteration of some part of the airway. These range from nasal strips,[1] through continuous positive airway pressure,[2] to resection of the soft palate and tracheostomy.[3] The latter forms of therapy are reserved for the snoring associated with obstructive sleep apnea.

Pharmacologic therapy of snoring is not mentioned in most reviews or is dismissed as not effective. Snoring has been linked with nasal congestion,[4] with gastroesophageal reflux (GERD)[5,6] and with reflux laryngitis[7]. We hypothesized that combined treatment of nasal congestion and GERD might have an impact on severe snoring. We chose pseudoephedrine sulfate, a nasal decongestant, and domperidone, a prokinetic agent used for adjuvant therapy of GERD. This study examines the impact of pseudoephedrine sulfate and domperidone combined in a single capsule on severe snoring, as well as the effects of each medication by itself.

Commentary Follows on Pages 26-27

METHODS

Study Subjects

This study was approved by the Ethical Committee of Clinica Central and by the Department of Clinical Studies of the Chilean Health Department. A convenience sample of 30 subjects whose partners complained of the patients' constant severe snoring of a degree requiring earplugs or separate bedrooms was recruited. These subjects were colleagues or acquaintances of the investigators and, by and large, had not sought medical attention for snoring or other symptoms. None had anatomic evidence of nasopharyngeal obstruction, as shown by nasopharyngoscopy. Their clinical characteristics are listed in Table 1. In Table 1, dysphonia refers to the hoarse voice often found in patients with reflux laryngitis. Apnea was considered present when sleeping partners reported brief periods of respiratory cessation and microarousal. No effort was made to quantify the number of episodes.

Study Design

This study combined data from 4 separate trials. An open-label trial of 60 mg of pseudoephedrine sulfate plus 10 mg of domperidone was followed by placebo-controlled double-blind trials of 60 mg of pseudoephedrine sulfate plus 10 mg of domperidone

Disclosure Statement
This was not an industry supported study. Dr. Larrain has created a firm, Faronacal Limited, for the development of psuedoephedrine sulfate and domperidone. Drs. Pope, Dominitz, and Ms. Hudson have indicated no financial conflicts of interest.

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Address correspondence to: Charles E. Pope, II, M.D., University of Washington, Box 356424; Seattle, WA 98195-6424; Tel: (206) 685-4098; Fax: (206) 685-8684; E-mail: popec@u.washington.edu

Table 1—Patient Characteristics

Pt. #	BMI	Heartburn	Throat clearing	Dysphonia	Apnea
1.	25	3	3	2	Yes
2.	22	1	No	No	No
3.	19	3	3	3	No
4.	25	3	3	3	Yes
5.	26	No	1	No	Yes
6.	28	1	3	3	Yes
7.	26	3	No	No	Yes
8.	24	1	No	No	Yes
9.	34	No	No	No	Yes
10.	26	3	No	No	Yes
11.	21	1	1	1	No
12.	35	1	1	No	No
13.	23	2	No	No	Yes
14.	27	1	2	No	Yes
15.	29	2	No	No	Yes
16.	28	3	3	No	Yes
17.	22	1	1	1	No
18.	25	3	3	2	Yes
19.	27	3	3	3	No
20.	42	2	No	No	Yes
21.	26	No	3	1	Yes
22.	48	2	3	2	No
23.	25	No	No	No	Yes
24.	27	1	2	No	No
25.	30	3	2	No	No
26.	32	No	2	No	Yes
27.	25	3	No	No	No
28.	27	1	3	2	No
29.	25	2	2	No	Yes
30.	29	2	No	No	No
A	28	2	1	1	Yes
B	22	3	1	1	Yes
C	31	1	No	No	Yes
D	26	1	No	No	Yes

BMI refers to body mass index; 1, aware of symptom, no medication intake; 2, occasional self-medication with over-the-counter drugs; 3, medical consultation, medical treatment.

Table 2—Results of Snoring Diaries for 30 Nights With the Use of Open-Label Pseudoephedrine (60 mg) Plus Domperidone (10 mg)

Patient	Days on Treatment, no.	Snoring Intensity* No. of Nights			
		No	Slight	Moderate	Severe
1.	30	30	0	0	0
2.	30	22	8	0	0
3.	30	23	5	0	2
4.	27	0	25	2	0
5.	24	0	10	11	3
6.	26	17	9	0	0
7.	29	19	10	0	0
8.	30	30	0	0	0
9.	30	0	27	3	0
10.	28	26	0	2	0
11.	18	1	11	5	1
12.	Drop out due to insomnia				
13.	29	27	2	0	0
14.	30	7	23	0	0
15.	28	24	3	0	1
16.	30	22	6	0	2
17.	30	27	3	0	0
18.	30	0	27	0	3
19.	Drop out due to palpitations				
20.	30	24	6	0	0
21.	30	29	0	1	0
22.	30	0	30	0	0
23.	27	18	8	1	0
24.	Drop out due to palpitations				
25.	30	30	0	0	0
26.	26	6	13	7	0
27.	30	26	2	2	0
28.	30	30	0	0	0
29.	30	28	1	0	1
30.	30	27	3	0	0
Total	772	493	232	34	13

*No refers to no snoring; slight, low-intensity snoring; Moderate, reduction in intensity but still bothersome; Severe, intolerable loud snoring.

versus placebo and 30 mg of pseudoephedrine sulfate plus 10 mg of domperidone versus placebo. Finally, a separate trial compared placebo with each of the medications alone and with the combination of these medications.

For the open-label trial, 30 subjects were given a capsule containing 60 mg of pseudoephedrine sulfate and 10 mg of domperidone All studies were done in the subjects' homes. The medication was taken one-half hour before bedtime. Their sleeping partners were given a diary and asked to evaluate the degree of snoring each night for a 30-day period. Each night received a rating of no snoring, slight snoring (low intensity, not bothersome), moderate snoring (reduction in intensity but still bothersome), or severe snoring (loud snoring interfering with the partner's sleep). These ratings were scored 0 to 3, with 0 indicating no snoring.

In the high-dose placebo-controlled trial, subjects recruited from the open-label trial received either 60 mg of pseudoephedrine sulfate plus 10 mg of domperidone or an identical placebo capsule. The low-dose trial compared 30 mg of pseudoephedrine sulfate plus 10 mg of domperidone with placebo. Randomization to study drug was performed using concealed allocation of treatment assignment. If a subject elected to enter both randomized double-blind trials, the subject might receive 2 placebos, 1 placebo and 1 active drug, or 2 different doses of active drug. Each group had 10 subjects; each trial lasted 10 days.

For the trial comparing the components with the drug mixture, 7 subjects from the original open-label trial were joined by 3 additional subjects with severe snoring. Following a 10-day placebo period, they were randomly assigned to either pseudoephedrine sulfate 60 mg or to domperidone 10 mg for a 10-day period. Subsequently, they received the other single agent for 10 days, followed by 60 mg of pseudoephedrine plus 10 mg of domperidone for 10 days. Each period was separated by 5 days.

Analysis

Snoring ratings were summated for each 10-day period. Scores for the active drug versus placebo were compared using the Wilcoxon rank sums test (SAS System for Windows Release 9.1, SAS Institute, Cary, NC). Snoring was also categorized as severe or not at any time during the 10-day period. This dichotomous outcome was evaluated using the χ^2 test. The Student paired t test was used for the trial of the drug components. A 2-tailed p value of $< .05$ was used to determine statistical significance without correction for multiple comparisons.

Table 3—Results of Snoring Diaries for 10 Nights for Subjects Taking Placebo or Pseudoephedrine (60 mg) Plus Domperidone (10 mg)

Placebo					Drug				
Patient	Snoring intensity*, no. of nights				Patient	Snoring intensity*, no. of nights			
	No	Slight	Moderate	Severe		No	Slight	Moderate	Severe
1.	0	0	0	10	4.	0	10	0	0
5.	0	0	4	6	6.	4	4	2	0
7.	0	0	1	9	8.	7	3	0	0
10.	0	0	0	10	9.	0	10	0	0
11.	0	0	2	8	13.	8	2	0	0
15.	0	0	0	10	14.	5	5	0	0
16.	0	0	1	9	18.	6	4	0	0
21.	0	0	0	10	20.	9	1	0	0
23.	0	0	0	10	22.	2	7	1	0
26.	0	0	0	10	A.	1	9	0	0
Total	0	0	8	92	Total	42	55	3	0

*No refers to no snoring; slight, low-intensity snoring; Moderate, reduction in intensity but still bothersome; Severe, intolerable loud snoring.

Table 4—Results of Snoring Diaries for 10 Nights for Subjects Taking Placebo or Pseudoephedrine (30 mg) Plus Domperidone (10 mg)

Placebo					Drug				
Patient	Snoring intensity*, no. of nights				Patient	Snoring intensity*, no. of nights			
	No	Slight	Moderate	Severe		No	Slight	Moderate	Severe
1.	0	0	0	10	7.	0	0	7	3
4.	0	0	0	10	8.	8	2	0	0
5.	0	0	0	10	10.	0	0	0	10
6.	0	0	0	10	11.	0	2	8	0
9.	0	0	0	10	14.	7	3	0	0
15.	0	0	0	10	18.	7	3	0	0
17.	0	0	2	8	21.	0	7	3	0
20.	0	0	0	10	23.	9	1	0	0
22.	0	0	0	10	24.	0	10	0	0
29.	0	0	1	9	26.	0	0	0	10
Total	0	0	3	97	Total	31	28	18	23

*No refers to no snoring; slight, low-intensity snoring; Moderate, reduction in intensity but still bothersome; Severe, intolerable loud snoring.

RESULTS

Table 2 presents the results of the open-label trial. Snoring was eliminated in 493 of the 772 nights evaluated and markedly improved in another 232 nights. Although snoring promptly recurred at the original intensity in most subjects, 7 subjects remained free from snoring for at least 6 to 8 weeks. Many subjects reported more energy and less drowsiness during the trial; no attempt was made to quantify these changes. Three subjects did not tolerate the study drugs. Two noted palpitations, and 1 suffered from insomnia.

Eighteen of the subjects in this trial had periods of witnessed apnea before entry into the trial. These apneic events disappeared in all of the subjects during the time they were taking active medication. After the completion of the trials, 6 of these subjects continued their medication; none had a return of witnessed apnea. Ten subjects did not continue on medication; 5 redeveloped witnessed apneic episodes, and 5 remained free from apneic events.

Results from the high-dose double-blind trial are shown in Table 3. Overall, snoring scores were significantly lower ($p = .001$), and severe snoring was markedly reduced in the actively treated group ($p < .0001$).

When the dose of pseudoephedrine sulfate was reduced to 30 mg (plus 10 mg domperidone), the same improvement was shown, although the results are less striking, as shown in Table 4. Again, snoring scores were significantly lower ($p = .007$), and severe snoring was markedly reduced in the actively treated group ($p < .001$). Of the patients entering both double-blind trials, 11 received a placebo in 1 trial and an active drug in the other. Comparing these trials with a paired t test, the 6 receiving the high-dose regimen had a mean improvement in their snoring score of 22.4 points (SD 3.8, $p = .0002$). The 5 patients receiving the low-dose regimen noted an improvement of 10.3 points over their placebo results; this did not reach statistical significance ($p = .07$).

The results of the trial of individual components of the drug combination are shown in Table 5. There is improvement of snoring with the single agents when compared with placebo ($p < .005$). The combination of the 2 agents was more effective when compared with pseudoephedrine sulfate alone ($p = .003$) and when compared with domperidone alone ($p = .0003$).

Table 5—Results of Snoring Diaries for 10 Nights for 10 Subjects Taking Placebo, Individual Drugs, and a Combination of Drugs

Patient	Placebo				Pseudoephedrine, 60 mg				Domperidone, 10 mg				Pseudoephedrine, 60 mg, plus domperidone, 10			
	Snoring intensity*, no. of nights															
	No	Slight	Moderate	Severe	No	Slight	Moderate	Severe	No	Slight	Moderate	Severe	No	Slight	Moderate	Severe
5	0	0	2	8	0	8	2	0	0	6	4	0	3	5	2	0
13	0	0	2	8	0	1	4	5	0	5	4	1	5	4	1	0
15	0	0	2	8	0	5	5	0	0	5	5	0	5	5	0	0
18	0	0	2	8	1	3	5	1	1	3	6	0	3	7	0	0
21	0	0	2	8	0	2	5	3	0	2	6	2	10	0	0	0
23	0	0	2	8	1	3	6	0	0	4	5	1	0	9	1	0
29	0	0	1	9	4	3	3	0	0	3	5	2	5	5	0	0
B	0	0	2	8	0	7	3	0	0	1	8	1	3	6	1	0
C	0	0	1	9	2	5	3	0	4	4	2	0	8	2	0	0
D	0	0	0	10	6	3	1	0	5	4	1	0	7	2	1	0
Total	0	0	16	84	14	40	37	9	10	37	46	7	49	45	6	0

*No refers to no snoring; slight, low-intensity snoring; Moderate, reduction in intensity but still bothersome; Severe, intolerable loud snoring.

DISCUSSION

Snoring is a worldwide phenomenon. The prevalence of snoring has been reported as 20% of the population in Sweden,[8] 32% in France,[9] 27% in Poland,[10] 29% in Denmark,[11] 23% in China,[12] and 33% in the United States.[13] Attempts to alleviate this universal problem have led to the large number of therapies mentioned earlier; clearly, no one form of therapy seems to be successful.

The present study was stimulated by the reports of patients of 1 of the authors who had noted disappearance of their snoring after successful antireflux surgery. The use of antireflux surgery to treat a common disorder such as snoring might be considered too radical a form of therapy. Therefore, we chose to use pseudoephedrine sulfate as a nasal decongestant and domperidone, a compound previously shown to have a modest effect on the treatment of GERD.[14,15] Domperidone does not cross the blood-brain barrier and is very well tolerated at an oral dose of 10 mg per day. Pseudoephedrine sulfate is readily available without a prescription. Severe hypertension and severe coronary disease are listed as contraindications; no cross-reactions with domperidone have been reported. In our study, 2 subjects reported palpitations at a dose of 60 mg of pseudoephedrine sulfate plus 10 mg of domperidone; 1 of these subjects tolerated 30 mg of pseudoephedrine sulfate plus 10 mg of domperidone.

The experimental design depended on reporting of snoring intensity by the sleeping partner of our subjects. Although some might suggest that this outcome variable is quite subjective, certainly cessation of snoring and, therefore, an uninterrupted sleep of the partner is clinically very important. Snoring quantification by sleeping partners is performed in the snorer's usual surroundings and requires no instrumentation. It has been shown that categorizing snoring as none, slight, moderate, and severe correlates moderately well with objective measurements of snoring frequency and intensity using a microphone.[16]

The open-label trial was performed first to see if a beneficial effect could be demonstrated. The encouraging results led to the double-blind trials to minimize a possible placebo effect. Those on placebo snored on with vigor; those unlucky enough to be assigned twice to the placebo arm showed good reproducibility of their snoring pattern. There was some improvement in the 30-mg pseudoephedrine sulfate group, and significant improvement in the 60-mg group, thus demonstrating a positive dose-response curve. Each of the 2 medications showed significant improvement when compared with placebo. The combination of drugs was more effective than either agent used alone. Though we can not exclude the possibility that medication side-effects led to unblinding of the treatment allocation, the magnitude of the response, even with a relatively small sample and the rating by the subjects' partners lead us to conclude that this is probably not a major limitation of the study.

What possible mechanisms exist that might help to explain these results? Nine of our subjects had reflux sufficiently marked to warrant more than casual treatments with intermittent antacids. Five subjects had no clinical evidence for reflux; their reflux status was not checked with pH monitoring. There is no evidence in these subjects that their individual reflux status changed during the study period. Domperidone may have other actions than its effect on reflux.

What are some limitations of this study? Quantification of snoring by bed partners is quite a subjective measure. However, sleeping partners can clearly recognize when the intensity of the snoring is high enough to awaken them. Is it possible that pseudoephedrine sulfate interfered with the subjects' sleep patterns and thus led to a decrease in snoring? Our subjects usually reported an increased feeling of well-being and decrease in daytime somnolence. However, a definitive answer awaits study of this drug combination in a sleep laboratory. Our study did not attempt to study sleep patterns such as sleep latency and arousal patterns; our attention was focused on snoring intensity only. This study did not investigate a large number of obese patients, although some of the subjects had elevated body mass indexes. It would have been interesting to study the subjects in a sleep laboratory; such a facility was not available to the investigators.

This study would suggest that the combination of pseudoephedrine sulfate and domperidone could be considered in those individuals whose partners report that the patients have severe snoring. We would suggest beginning with a dose of 60 mg of pseudoephedrine sulfate and 10 mg of domperidone combined in the same capsule. The dose of pseudoephedrine sulfate could be lowered to 30 mg if the first combination produced side effects, although this dose is not as effective as is the 60-mg dose. Our study was only 30 days in length. It is possible that the individuals taking this combination may develop tolerance or tachyphylaxis over longer periods of treatment. Only longer studies will confirm or refute this possibility.

It has been shown when both partners are in a sleep lab at the same time, treatment of snoring in the patient leads to a better quality of sleep in the partner.[17] Reduction of snoring may thus lead to a better quality of life for both the snorer and his or her partner. We look forward to further studies to evaluate the mechanism or mechanisms of this drug combination and to studies attempting to quantify other health benefits following the treatment of severe snoring.

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