Does Pseudoephedrine Increase Blood Pressure in Patients with Controlled Hypertension?

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Background. The use of the decongestant pseudoephedrine has been avoided in hypertensive patients with little evidence to support this caution. The purpose of this study was to determine the effects of therapeutic doses of pseudoephedrine on blood pressure in patients with controlled hypertension.

Methods. Twenty-five patients with controlled hypertension were enrolled in a randomized, placebo-controlled, double-blind crossover trial. This was a 4-week study in which all participants received placebo during the 1st and 3rd weeks. Subjects were randomly assigned to receive pseudoephedrine or placebo during the 2nd week of the study, and to receive the opposite during the 4th week of the study. Blood pressure readings were taken at the beginning and end of each week of the trial, and at a 1-week poststudy follow-up visit.

Results. The mean systolic pressure was 133 mm Hg i patients receiving both pseudoephedrine and placeb (*P*=NS). The mean diastolic pressure was 82 mm Hg i patients receiving pseudoephedrine and 82.5 mm Hg i patients receiving placebo. Mean pulse rates were 76. and 75.2 beats per minute in patients given pseudo ephedrine and those given placebo, respectivel (*P*=NS). There were no statistically significant or clin cally important differences in the mean systolic or mea diastolic blood pressures among the groups during th entire 4-week course of the study.

Conclusions. At standard doses, pseudoephedrine has n significant effect on systolic or diastolic blood pressur in patients with controlled hypertension.

Key words. Pseudoephedrine; hypertension; vasocon strictor agents, nasal. (*J Fam Pract 1995; 40:22-26*)

Pseudoephedrine, the L-isomer of ephedrine, was isolated in 1889 and introduced for therapy in 1924.[1,2] This sympathomimetic decongestant is frequently used in over-the-counter cough and cold preparations. The safety of using this medication in persons with hypertension has been questioned. Physicians are cautioned about its use in the package inserts, the American Hospital Formulary Service publication *Drug Information*,[3] *Physicians' Desk Reference*,[4] and other publications.[5] Since approximately 50 million Americans are hypertensive,[6] the safety of this commonly used over-the-counter medication is an important issue.

Clinical trials of the effect of decongestants on blood pressure have produced a range of conflicting results Only a few studies have addressed the effect of pseudo ephedrine on blood pressure,[8–15] and only three of thes studies have examined its effect on hypertensive pa tients[13–15] (Table 1). One of these studies, a doubl blind, randomized crossover trial, looked at a single dos that produced a statistically significant increase in systoli blood pressure but no significant change in diastoli blood pressure.[13] Another study, an uncontrolled tri that looked at the combination of a substandard dose o pseudoephedrine (65 mg every 12 hours) with an antihis tamine, found no increase in blood pressure.[14] A recen study evaluated the use of pseudoephedrine for 3 days i a double-blind, placebo-controlled trial in patients wit controlled hypertension,[15] and found no effect on bloo pressure. The short duration (3 days) and low statistica power of the study (49% for systolic and 63% for diastolic prevented any firm conclusions.

The purpose of this study was to measure the effect o

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Table 1. Summary of Three Previous Studies of Pseudoephedrine in Hypertensive Patients

Authors	Year	Sample Size, Active/ Placebo	Study Design	Therapy Studied	Controlled Hypertension	No. of Subjects Taking Antihypertensives	Mean Difference* (mm Hg)	
							Systolic	Diastolic
Chua et al[13]	1989	20/20	Double-blind randomized, placebo-controlled, crossover	Single dose of pseudoephedrine (60 mg) vs placebo	Unknown	11	2.9†	1
Greening[14]	1969	21/21	Unblinded nonrandomized crossover	Sustained-release pseudoephedrine (65 mg) plus chlorpheniramine bid for 3 to 14 days	No	13	None	None
Bradley et al[15]	1991	13/12	Double-blind randomized, placebo-controlled	3 Days of qid pseudoephedrine (60 mg) vs placebo	Yes	25	−2	−1

**Positive differences indicate higher mean pressure with pseudoephedrine therapy and negative differences indicate lower mean pressure with pseudoephedrine therapy.*
†$P<.03$.

therapeutic doses of pseudoephedrine on blood pressure in patients with controlled hypertension in a double-blind, placebo-controlled, randomized crossover trial.

Methods

At the time of enrollment, each subject gave informed consent using a form approved by the University of Virginia Human Investigation Committee. Each was given an instruction summary sheet with directions, schedules, and precautions.

The 4-week study was designed to begin with all subjects receiving placebo for the 1st week. Two placebo lactose tablets that were identical in appearance and taste to the 30-mg pseudoephedrine tablets were given at 8 AM, noon, 4 PM, and 8 PM. The 30-mg tablet was used because it is the most frequently prescribed tablet size of pseudoephedrine. The subjects were randomly assigned to receive either a placebo (two tablets) or pseudoephedrine (two 30-mg tablets) on the same schedule during the 2nd week. All subjects received placebo again during the 3rd week. During the 4th week, subjects were crossed over to receive the other study medication (eg, patients receiving placebo during week 2 received pseudoephedrine during week 4). Randomization was carried out by the central pharmacy using a random number table, and the code was kept there until completion of the study.

Throughout the 4-week study, blood pressure was measured weekly. All subjects had an additional blood pressure measurement 1 week after the trial was concluded. At each visit, patient weight, pulse rate, and blood pressure were noted. Average blood pressure was based on three readings conducted under similar circumstances: patients were in a sitting position; the same arm, sphygmomanometer cuff, and operator were used at each visit; and each patient's appointments took place at the same time and on the same day of the week.

Side effects were recorded, and pills were counted at each visit to establish an index of compliance. Each week the subjects were asked whether they knew which treatment they were receiving (placebo or active). Each subject was given a 3-month supply of his or her hypertension medication as compensation (monetary equivalent $10 to $200) for participation in the study.

Subjects

To meet enrollment criteria, patients had to have medically controlled hypertension with systolic blood pressure ≤140 mm Hg and diastolic blood pressure ≤90 mm Hg for at least 6 weeks before enrollment.[6] The age range for enrollment was 18 to 70 years. Exclusion criteria included (1) a history of coronary artery disease, (2) a history of cerebral vascular disease, (3) a history of allergy to pseudoephedrine, (4) current treatment with a monoamine oxidase inhibitor, and (5) a history of noncompliance with medical therapy.

Statistical Analysis

The data were analyzed based on methods for a two-period changeover design,[16] which results in a comparison of the sum of blood pressures for weeks 1 and 3 between study periods to test for carryover effects using a

two-sample t test between groups.[17] Using this design, if the test for changeover effects is not significant, then a test for drug effect reduces to a simple two-sample t test for the difference in blood pressure response for weeks 2 and 4 between the study groups.

Since both systolic and diastolic blood pressures were skewed to the right, these data were transformed using a logarithmic transformation. Based on data from the Framingham study,[18] the transformation used for systolic blood pressure was $\log_{10}[(SBP-75)/25]$. Although a similar transformation for diastolic blood pressure has not been identified, we used log(DBP). The data were initially analyzed without transformation.

Before the study, sample size was selected to yield a 90% power to reject the hypothesis of no drug effect if the true drug-related change in systolic or diastolic blood pressure was 5 mm Hg or more with a two-tailed α level of .05.[19] This assumes a standard deviation of 7 mm Hg as seen in a previous study of pseudoephedrine in hypertensive patients.[13] Twenty-one subjects were needed to achieve this power. Power was calculated on nontransformed data.

Table 2. Characteristics of Subjects in the Pseudoephedrine Study Crossover Groups

	Group Taking Drug First (n=13)	Group Takin Placebo Firs (n=12)
Race, n		
Black	8	6
White	5	6
Sex, n		
Female	9	7
Male	4	5
Daily smoker, n	1	1
Uses caffeine daily, n	7	8
Uses alcohol daily, n	2	3
Antihypertensive medications used, n		
Diuretic	4	7
ACE inhibitor	8	3
Calcium channel antagonist	4	7
Mean age, y	52.1	48.5

Results

Sixteen female and nine male hypertensive patients from the University of Virginia Family Medicine Clinic in Charlottesville participated in the study. Patient ages ranged from 31 to 68 years (mean 50.4 years), and weight ranged from 122 to 265 lb (55.5 to 120.0 kg), with a mean of 197 lb (89.5 kg). Fourteen patients were black and 11 were white. There were no substantial differences between the two crossover groups as randomized (Table 2).

All patients maintained their individual antihypertensive regimen throughout the study. No attempt was made to exclude a patient because of the type of antihypertensive agent used. The comorbid conditions of the enrolled subjects were: type II diabetes mellitus (4), hyperlipidemia (5), peptic ulcer disease (3), and gout (1).

All 25 persons who entered the study completed the protocol and were included in the statistical analysis. Based on the weekly pill count, compliance throughout the study in all groups averaged 95%.

Two of 25 subjects complained of possible side effects during the 25 pseudoephedrine weeks (one was anxious and one was drowsy). Eleven of the 25 subjects had symptoms during the 75 placebo weeks (three with headaches, two with fatigue, one with anxiety, and one each with dizziness, urinary frequency, insomnia, transient sharp chest pain, and backache). Subjects correctly identified the active and placebo weeks 62% of the time durin the 2 unknown weeks.

No significant change in mean systolic (P=NS) diastolic (P=NS) was observed during administration pseudoephedrine (Figure). These results were unchang using logarithmic transformations of the data. The mea systolic pressure was 133 mm Hg with the administrati of both pseudoephedrine and placebo. The mean di stolic pressure was 82 mm Hg with pseudoephedrine an 82.5 mm Hg with placebo. The mean pulse rate durin pseudoephedrine administration was 76.8 beats p minute as compared with 75.2 beats per minute durin placebo administration (P=NS).

Discussion

Currently, the package insert for pseudoephedrine ca tions against its use in hypertensive persons.[4] The findin of this study, however, support the safety of using th usual clinical dosage of pseudoephedrine for up to 1 wee in patients with controlled hypertension not associate with major cardiovascular or cerebral vascular diseas There was 0 mm Hg change (standard deviation [SD 4.06 mm Hg) in the mean systolic pressure, and only −0.5 mm Hg change (SD, 2.8 mm Hg) in the mea diastolic pressure between the pseudoephedrine and th placebo periods. Based on collected data in this study, recalculation of power indicates that the sample size this trial allowed more than 90% power to reject the h

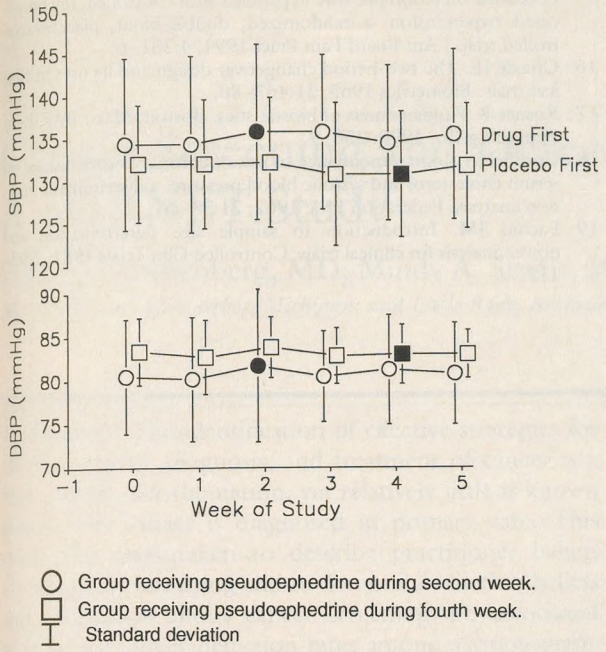

Figure. Mean systolic and diastolic blood pressure readings (± standard deviation) for patients in the group taking pseudoephedrine during the 2nd week and those in the group taking the medication during the 4th week. Shaded symbols indicate the week pseudoephedrine was administered to that group.

pothesis of no drug effect if the true drug-related change in either systolic or diastolic blood pressure was 5 mm Hg or more. Smaller changes than this for such brief periods are believed to have little clinical significance.

The results of this study strongly support two previous studies that showed no effect of pseudoephedrine on blood pressure.[14,15] These two studies had lower statistical power, however, and one studied patients with uncontrolled hypertension, giving only one half of the usual dose of pseudoephedrine.[14] A third study[13] reported a statistically significant 2.9 mm Hg increase in systolic pressure and a 1.0 mm Hg increase in diastolic pressure (*P*=NS), as well as an increase in mean pulse rate of 3.4 beats per minute, after a single dose of pseudoephedrine, which is not usually administered as a single dose. In that study, the authors commented that these changes were not associated with any clinical symptoms. The difference in results with a single dose vs multiple therapeutic doses may be associated with tolerance developing with repeated doses.

It should be noted that the patients in our study were receiving three types of antihypertensive agents: ACE inhibitors, calcium channel antagonists, and diuretics. The results may not be generalizable to patients taking other types of antihypertension agents. The mean weight of our study population was probably greater than the mean for the hypertensive population. All of the subjects in this study were well motivated, with documented compliance with previous medical therapies. Because they came from the same practice, which has consistent and well-documented medical care, the investigators had access to all their medical records and were able to confirm that their blood pressure was controlled.

Conclusions

This study demonstrated that standard clinical doses of oral pseudoephedrine (60 mg four times daily) have no significant effect on systolic or diastolic blood pressure in patients with controlled hypertension when used for 1 week. These results may not apply to patients with uncontrolled hypertension. Although the results are significant, a much larger study involving these and other antihypertension agents may be necessary to enhance generalizability.

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References

1. Chua SS, Benrimoj SI. Non-prescription sympathomimetic agents and hypertension. Med Toxicol 1988; 3:393–7.
2. Chopra RN, Krishna S, Ghose TP. Ephedrine and pseudoephedrine, BMJ 1931; 2:906.
3. AHFS drug information. Bethesda, Md: American Society of Hospital Pharmacists, 1993.
4. Physicians' desk reference for nonprescription drugs. Oradell, NJ: Medical Economics, 1993:541.
5. Boyd JR. Pseudoephedrine. Am Pharm 1986; NS26(11):746–8.
6. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, Md: US Department of Health and Human Services, National Institutes of Health, 1993. NIH Publication No. 93–1088.
7. Radack K, Deck CC. Are oral decongestants safe in hypertension? An evaluation of the evidence and a framework for assessing clinical trials. Ann Allergy 1986; 56:396–401.
8. Chen KK. A comparative study of ephedrine, pseudoephedrine and phenyl-ethylamine. Arch Intern Med 1927; 39:404–11.
9. Drew DDM, Knight GT, Hughes DTD, Bush M. Comparison of the effects of D-(−)-ephedrine and L-(+)-pseudoephedrine on the cardiovascular and respiratory systems in man. Br J Clin Pharmacol 1978; 6:221–5.
10. Empey DW, Young GA, Letley E, John GC, Smith P, McDonnell KA, et al. Dose-response study of the nasal decongestant and cardiovascular effects of pseudoephedrine. Br J Clin Pharmacol 1980; 9:351–8.
11. Empey DW, Bye C, Hodder M, Hughes DTD. A double-blind

crossover trial of pseudoephedrine and triprolidine, alone and in combination, for the treatment of allergenic rhinitis. Ann Allergy 1975; 34:41–6.
12. Saunders A, Elliott P. Pseudoephedrine in the hypertensive patient. Aust J Hosp Pharm 1987; 17:150–2.
13. Chua SS, Benrimoh SI, Gordon RD, Williams G. A controlled clinical trial on the cardiovascular effects of single doses of pseudoephedrine in hypertensive patients. Br J Clin Pharmacol 1989; 28: 369–72.
14. Greening GK. The effect of an antihistamine-pseudoephedrine drug on the blood pressure of moderate hypertensives. Curr Ther Res 1969; 11:252–5.
15. Bradley JG, Kallail KJ, Dorsch JN, Fox J. The effect of pseudoephedrine on blood pressure in patients with controlled, uncomplicated hypertension: a randomized, double-blind, placebo-controlled trial. J Am Board Fam Pract 1991; 4:201–6.
16. Grizzle JE. The two-period changeover design and its uses in clinical trials. Biometrics 1965; 21:467–80.
17. Rosner B. Fundamentals of biostatistics. Boston, Mass: PWS-Kent Publishing Co, 1990: 250–9.
18. Cornfield J. Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure: a discriminant function analysis. Federation Proc 1962; 21:58–61.
19. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Controlled Clin Trials 1981; 2:93–113.