

The Effect Of Pseudoephedrine On Blood Pressure In Patients With Controlled, Uncomplicated Hypertension: A Randomized, Double-Blind, Placebo-Controlled Trial

John G. Bradley, M.D., Ken J. Kallail, Ph.D., John N. Dorsch, M.D., and Joan Fox, R.N.

Abstract: Pseudoephedrine is frequently used as a decongestant. Because of concern about the safety of pseudoephedrine in hypertensive patients, a clinical trial was conducted to determine whether blood pressure control was actually affected by this drug in a selected group of patients with hypertension. Twenty-nine patients with controlled, uncomplicated hypertension, who received drug therapy and ranged in age from 25 to 50 years, were randomized to a treatment or a control group. Subjects took either 60 mg of pseudoephedrine or placebo capsules four times a day for 3 days. From 0800 hours until 2200 hours each day, the subjects obtained hourly blood pressure measurements using a portable sphygmomanometer. An analysis of variance with repeated measures was calculated to determine group differences for systolic and diastolic readings. No statistically or clinically significant differences were found. Therapeutic doses of pseudoephedrine did not adversely affect control of hypertension in these selected patients. (J Am Board Fam Pract 1991; 4:201-6.)

Pseudoephedrine, phenylpropanolamine, and phenylephrine are oral sympathomimetic agents commonly used as decongestants in prescription and over-the-counter preparations. Long-standing concern exists regarding their potential adverse effect in hypertensive patients. This concern is found in standard texts (e.g., *American Hospital Formulary Service—Drug Information*),¹ prescribing information, package labeling, and the literature.^{2,3} Given the ubiquity of the problems for which these drugs are used, the availability of these drugs, and the high rate of hypertension in this country,⁴ sufficient information about their effects in hypertensive patients is important. Little data, however, are available.

Phenylpropanolamine, while probably safe at recommended doses in persons with normal blood pressures,⁵⁻⁷ has been the subject of great concern.^{8,9} It has been evaluated in only one study

in hypertensive patients. While no adverse effect was found,¹⁰ this study was uncontrolled, a combination of drugs was used, and patient compliance was unverified. Only topical nasal administration of phenylephrine has been studied in hypertensive patients. In one double-blind study, no elevation of blood pressure was found when doses exceeded therapeutic levels.¹¹ Researchers in other similar studies have failed to show increased blood pressure resulting from nasally administered phenylephrine.²

Data from studies of oral pseudoephedrine given to persons with normal blood pressure have shown no clinical effect on blood pressures when administered in amounts double or higher than the therapeutic dose.¹²⁻¹⁴ Isolated reports exist of hypertensive crises or elevated blood pressure measurements in patients taking pseudoephedrine, but these patients were taking overdoses or combination drugs.²

Two studies have assessed the effect of pseudoephedrine on blood pressure in hypertensive patients. Findings from one study showed no adverse effect, but the study was uncontrolled and combination drugs were used.¹⁵ The other study was a crossover, double-blind trial using single oral doses of pseudoephedrine. Statistically significant elevations in blood pressure were found;

From the Department of Family and Community Medicine, University of Kansas School of Medicine-Wichita, and the St. Joseph Medical Center Family Practice Residency, Wichita. Address reprint requests to John G. Bradley, M.D., SIU Decatur Family Practice Residency, 1314 North Main, Suite 201, Decatur, IL 62526.

This project was supported by grants from the American Academy of Family Physicians Foundation and the Family Health Foundation of Kansas.

however, these elevations were not clinically significant based on the reported data.¹⁶

The literature review and clinical experience support that pseudoephedrine at therapeutic doses might be a safe drug in at least some hypertensive patients. The efficacy of pseudoephedrine as a nasal decongestant has been reported,^{13,17} and evaluations of its effect on hypertension have been called for by some authors.^{2,3}

The purpose of our study was to test the hypothesis that repeated maximal therapeutic doses of immediate-release oral pseudoephedrine would not adversely affect control of uncomplicated hypertension in selected patients. The study was undertaken in the hope that the findings would assist physicians with their recommendations to hypertensive patients regarding pseudoephedrine.

Methods

Twenty-nine persons were enrolled in the study after meeting eligibility requirements and providing informed consent. Sixteen were recruited from a residency teaching practice, 7 from a private practice, and 6 through an advertisement. Four were eventually excluded from data analysis (see below).

To be eligible, subjects (1) had to have previously diagnosed hypertension; (2) had to be receiving drug therapy; (3) had to have documented office blood pressure measurements of 140/90 mmHg or less on the day of enrollment and for at least 1 month before enrollment (this criterion reflects the standard decision-making practice related to hypertension control); (4) could range in age from 18 to 50 years; (5) could not have histories of diabetes or cerebrovascular, cardiovascular, or peripheral vascular disease; and (6) had to be deemed reliable and compliant by their personal physician.

Patients taking α -blockers or a combination of α - and β -blockers were excluded. With the patient's permission, the subject's physician verified the patient's clinical data.

The number and type of antihypertensive drugs used by the 25 persons completing the study are shown in Table 1. The medical records of the 5 patients who were taking two or three antihypertensive drugs were reviewed to determine whether they experienced less blood pres-

Table 1. Antihypertensive Drugs Taken by the 25 Patients Completing the Study.

Drug	Number of Patients
Diuretics	
Hydrochlorothiazide	8
Chlorthalidone	2
Triamterene	2
Amiloride	1
β -Blockers	
Atenolol	4
Pindolol	2
Propranolol	1
Angiotensin-converting enzyme inhibitors	
Lisinopril	7
Enalapril	3
Captopril	1
Calcium channel blockers	
Verapamil	2
Diltiazem	1
Peripheral vasodilators	
Hydralazine	1
Patients taking one antihypertensive drug	20*
Patients taking two antihypertensive drugs	4
Patient taking three antihypertensive drugs	1

*Patients taking combination diuretics were counted in this group.

sure control than those taking only one drug. The hypertension of all subjects appeared to be controlled, and blood pressure measurements met the criteria for inclusion in the data analysis.

Subjects were randomized in a double-blind fashion to a control or a treatment group. Placebo (lactose) and 60-mg pseudoephedrine capsules used in the investigation were manufactured by the hospital pharmacy. All capsules were identical and self-administered on 3 consecutive days at 0800, 1200, 1600, and 2000 hours. A 60-mg dose to be taken four times a day was used because it is the maximum recommended therapeutic dose. A 3-day study period was selected to provide adequate time for steady-state serum levels and to enhance the likelihood of any adverse effect on blood pressure control.

Subjects were provided a small portable oscillometric sphygmomanometer (Marshall 85™) with automatic digital readout, and they were taught to obtain their own blood pressure meas-

urements according to American Heart Association guidelines.¹⁸ The technique for insuring accuracy of the sphygmomanometer had been reported previously.¹⁹ Using this method,¹⁹ sphygmomanometer measurements for the current study were compared for accuracy simultaneously with those obtained from a standard calibrated wall-type mercury manometer. All measurements from the Marshall 85™ sphygmomanometer were within 5 mmHg of those obtained from the mercury manometer.

Subjects were given a 1-page data form to record the exact time each capsule was taken and values for each blood pressure measurement. They were to measure and record their blood pressure measurements hourly from 0800 to 2200 on each of the 3 study days. Subjects were instructed to notify the physician investigators immediately if their blood pressure exceeded 145 mmHg systolic or 94 mmHg diastolic. The subjects also were instructed to continue their regular prescription medications and normal activities during the trial. Compliance was assessed from the data form, history, and pill count at the end of the study period. A stipend was provided for patient participation.

Results

Twenty-five persons, ranging in age from 25 to 50 years, completed the protocol and were included in the data analysis. Two subjects (one in each of the treatment and control groups) deviated sufficiently from the protocol to be excluded. Two others reported a blood pressure measurement greater than 145/94 mmHg and were instructed to stop taking the study medication (one had taken only one capsule, and the second had taken six capsules). Both subjects continued to check their blood pressures hourly for 3 days and appeared to have uncontrolled hypertension, even though they had several previously documented office blood pressure values that were well within acceptable range. Both patients had been randomized to the control group and were taking a placebo.

Figure 1 displays the average blood pressure measurements of the pseudoephedrine and placebo groups for each of the 45 hourly readings in the 3-day period. An analysis of variance with repeated measures was calculated to determine group differences for both systolic and diastolic

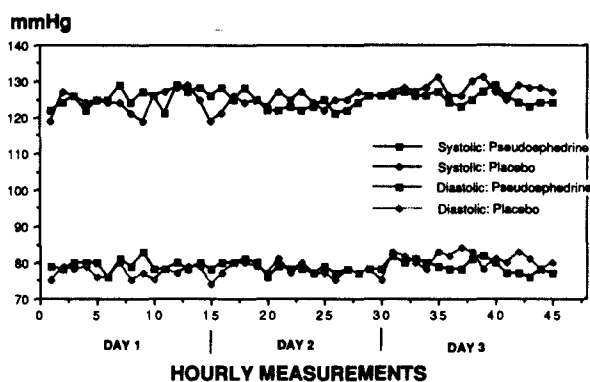


Figure 1. Average blood pressure measurements for each of the 45 hourly readings over 3 days.

readings. No differences were found for systolic ($F = 1.0$; $df = 44$) or diastolic ($F = 1.17$; $df = 44$) blood pressure measurements between the two groups ($P > 0.05$).

Table 2 shows the means, ranges, and standard deviations for systolic and diastolic blood pressures for the pseudoephedrine and placebo groups. Mean scores reflect well-controlled blood pressures throughout the study. The range of measurements, however, exceeded the allowable 145/94 mmHg established for safety.

As mentioned, subjects were instructed to call the physician investigators immediately if the systolic pressure exceeded 145 mmHg or the diastolic pressure exceeded 94 mmHg. Of those completing the study, 11 (5 in the pseudoephedrine group and 6 in the placebo group) failed to comply with these instructions. Of the 1125 hourly measurements, the allowable blood pressure level was exceeded 36 times (3.2 percent of total number of measurements). The systolic measurement exceeded 145 mmHg on six occasions (0.5 percent of total number of measure-

Table 2. The Means, Ranges, and Standard Deviations for Systolic and Diastolic Blood Pressure Measurements for Pseudoephedrine (n = 13) and Placebo (n = 12) Groups.

Blood Pressure	Pseudoephedrine mmHg	Placebo mmHg
Mean systolic	125	127
Range	95–146	74–161
Standard deviation	9.4	11.2
Mean diastolic	79	80
Range	55–111	53–111
Standard deviation	7.7	8.6

ments). The diastolic measurement exceeded 94 mmHg on 29 occasions (2.6 percent of total number of measurements). Both systolic and diastolic measurements exceeded the allowable level on one occasion.

Of the 36 occasions of high blood pressure measurements, 12 were reported by subjects taking pseudoephedrine and 24 were reported by subjects taking placebo (Table 3). The placebo group, therefore, had significantly more occasions of high blood pressure measurements ($\chi^2 = 4.5$; $df = 1$; $P < 0.05$). Three occasions of a high diastolic blood pressure and one occasion of high systolic and diastolic blood pressure were reported by one subject in the placebo group. He was a fireman who recorded these measurements during a 4-hour period while working at a fire.

Five persons in the pseudoephedrine group reported seven instances of side effects. The side effects included sleeplessness (2 subjects), decreased appetite (2 subjects), a funny taste in the mouth, increased thirst, and dry mouth. No one in the placebo group reported side effects.

Discussion

The purpose of this study was to evaluate the effect of pseudoephedrine on blood pressure con-

trol in hypertensive patients. The study was designed to obtain information that would be directly applicable to the outpatient family practice population.

All subjects were patients who had a high probability of having true hypertension. Antihypertensive medications were not discontinued to verify the patients' hypertension. Hypertension control was based on office blood pressure measurements documented in the patient's chart and taken at the time of enrollment. That both treatment and placebo groups experienced blood pressures greater than 145/94 mmHg raises the question of whether it is appropriate to rely solely on office blood pressure measurements in therapeutic decision making, which is the current method commonly used to assess hypertension control. Although this finding does not invalidate the conclusions of the study because similar results occurred in both groups, it does point out the need for further study of patients' ambulatory blood pressure measurements as they relate to control of hypertension.

The conclusions based on the results of this study are limited. Nevertheless, the subject selection procedures and the evaluation of the effect of pseudoephedrine on hypertension control were

Table 3. Summary of Patients Who Reported Blood Pressures > 145/94 mmHg during the Study Period.*

Group	Concurrent Medication(s)	Episodes of Elevated Blood Pressure	Highest Systolic Pressure mmHg	Highest Diastolic Pressure mmHg
Pseudoephedrine	Pindolol	1	144	97
Pseudoephedrine	Diltiazem	1	146	86
Pseudoephedrine	Hydrochlorothiazide Triamterene	1	135	95
Pseudoephedrine	Hydrochlorothiazide Lisinopril Verapamil	7	135	99
Pseudoephedrine	Hydrochlorothiazide Enalapril	2	144	97
Placebo	Hydrochlorothiazide	3	139	100
Placebo	Lisinopril	2	140	99
Placebo	Enalapril	7	142	105
Placebo	Lisinopril Hydralazine	3	161	100
Placebo	Chlorthalidone	6	148	111
Placebo	Hydrochlorothiazide Triamterene Captopril	3	150	92

*Highest systolic and highest diastolic measurements often did not occur together.

realistic and practical. We followed a reasonable clinical decision-making process that physicians regularly use to determine whether a patient has hypertension and whether the patient's hypertension is controlled.

A wide range of antihypertensive medications was used by patients in this study. All receiving α -blocker agents were specifically excluded, because of theoretic concern that pseudoephedrine would directly antagonize these drugs and, therefore, be less safe. No other attempts were made to control for the type of medications used.

The results show that pseudoephedrine did not adversely affect control of hypertension statistically or clinically. Whereas the number of subjects was small, the results suggest that, even with a greater number, no clinically significant differences would exist between the two groups. That the differences in group blood pressure measurements were small, that there were few occasions of high blood pressure measurements, and that most blood pressure elevations $> 145/94$ mmHg were in the placebo group support this conclusion. Further, elevations in blood pressure $> 145/94$ mmHg were generally not extreme.

Our results differed slightly from those of Chua and colleagues¹⁶ who reported some elevation of systolic blood pressure with one 60-mg dose of pseudoephedrine. They found no differences for diastolic blood pressures or mean arterial pressures. Although the differences in systolic measurements were statistically significant, these differences did not appear to be clinically important based on the data reported. The highest mean systolic pressure reported in this study was 134 mmHg with pseudoephedrine and 131 mmHg with placebo. The standard deviations for the blood pressure measurements for each treatment also were similar. Further, 9 of the 20 subjects studied were treated with low-salt diet alone and were not receiving drug therapy.¹⁶

An additional note of interest in our study involved the two patients who were poorly controlled according to ambulatory measurements and were excluded from analysis. They appeared to be controlled based on several office blood pressure measurements; however, ambulatory measurements strongly suggested otherwise.

Office measurements are generally believed to be higher than those taken elsewhere.²⁰ The occurrence of ambulatory blood pressure elevations

and good office control may be an unrecognized problem and an area for further investigation. It also highlights the difficulty of comparing office measurements with ambulatory measurements. Normative ambulatory data are difficult to obtain, and a certain percentage of ambulatory blood pressures $> 140/90$ mmHg is probably normal.^{21,22} For this reason, we compared the blood pressures of the two study groups and did not investigate the potential change in blood pressure from the entry criteria (i.e., office measurements).

Conclusion

Short-term administration of therapeutic doses of pseudoephedrine can be safe in a selected group of patients with controlled and uncomplicated hypertension. It should not be assumed, however, that pseudoephedrine will have no effect on patients with untreated hypertension. No specific age generalizations can be made based upon these data because of the small sample. Additional study is required to determine the safety of pseudoephedrine in other populations of patients with hypertension.

The authors acknowledge the valuable assistance of Dr. Randall V. Goering and Dr. Edward J. Hett in the completion of this project.

References

1. McEvoy GK, editor. AHFS drug information. Bethesda, MD: American Society of Hospital Pharmacists; 1990:648-54.
2. Chua SS, Benrimoj SI. Non-prescription sympathomimetic agents and hypertension. *Med Toxicol Adverse Drug Exp* 1988; 3:387-417.
3. 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.
4. National High Blood Pressure Education Program, Coordinating Committee. The 1988 report of the joint national committee on detection, evaluation, and treatment of high blood pressure. Bethesda, MD: National Heart, Lung, and Blood Institute, 1988. (NIH publication no 88-1088.)
5. Liebson I, Bigelow G, Griffiths RR, Funderburk FR. Phenylpropranolamine: effects on subjective and cardiovascular variables at recommended over-the-counter dose levels. *J Clin Pharmacol* 1987; 27:685-93.
6. Blackburn GL, Morgan JP, Lavin PT, Noble R, Funderburk FR, Istfan N. Determinants of the pressor effect of phenylpropranolamine in healthy subjects. *JAMA* 1989; 261:3267-72.

7. Goodman RP, Wright JT Jr., Barlaschini CO, McKenney JM, Lambert CM. The effect of phenylpropanolamine on ambulatory blood pressure. *Clin Pharmacol Ther* 1986; 40:144-7.
8. Bravo EL. Phenylpropanolamine and other over-the-counter vasoactive compounds. *Hypertension* 1988; 11(Suppl):II7-10.
9. Pentel P. Toxicity of over-the-counter stimulants. *JAMA* 1984; 252:1898-903.
10. Unger DL, Unger L, Temple DE. Effect of an anti-asthmatic compound on blood pressure of hypertensive asthmatic patients. *Ann Allergy* 1967; 25:260-1.
11. Myers MG, Iazzetta JJ. Intranasally administered phenylephrine and blood pressure. *Can Med Assoc J* 1982; 127:365-8.
12. Drew CD, Knight GT, Hughes DT, 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.
13. 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. *J Clin Pharmacol* 1980; 9: 351-8.
14. Bye C, Hill HM, Hughes DTD, Peck AW. A comparison of plasma levels of L-(+)pseudoephedrine following different formulations, and their relation to cardiovascular and subjective effects in man. *Eur J Clin Pharmacol* 1975; 8:47-53.
15. Greening GK. The effect of an antihistamine-pseudoephedrine drug on the blood pressure of moderate hypertensives. *Curr Ther Res* 1969; 11:252-5.
16. Chua SS, Benrimoj 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.
17. Empey DW, Bye C, Hodder M, Hughes DT. 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.
18. Kirkendall WM, Feinleib M, Freis ED, Mark AL. Recommendations for human blood pressure determination by sphygmomanometers. Subcommittee of the AHA Postgraduate Education Committee. *Circulation* 1980; 62:1146A-1155A.
19. Bradley JG, Dorsch JN, Kallail KJ, Chaney EJ, Haskins RJ, Streit JG. The accuracy of the Marshall 85 oscillometric sphygmomanometer in the ambulatory care setting. *J Am Board Fam Pract* 1989; 2: 247-51.
20. Spence JD. Pseudohypertension. In: Laragh JH, Brenner BM, editors. *Hypertension: pathophysiology, diagnosis and management*. Vol. 2. New York: Raven Press, 1990:1407-14.
21. Drayer JI, Weber MA, Nakamura DK. Automated ambulatory blood pressure monitoring: a study in age-related normotensive and hypertensive men. *Am Heart J* 1985; 109:1334-8.
22. Kennedy HL, Horan MJ, Sprague MK, Padgett NE, Shriver KK. Ambulatory blood pressure in healthy normotensive males. *Am Heart J* 1983; 106:717-22.