Br. J. clin. Pharmac. (1989), **28**, 369–372

A controlled clinical trial on the cardiovascular effects of single doses of pseudoephedrine in hypertensive patients

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Twenty hypertensive patients received single oral doses of pseudoephedrine 60 mg or placebo in a double-blind, randomised, crossover trial. Systolic, diastolic, mean arterial blood pressure, and heart rate were measured at 5 min intervals for 30 min prior to and 210 min after the administration of pseudoephedrine or placebo. Statistically significant differences between the two treatments were observed with changes in systolic blood pressure ($P < 0.03$) and heart rate ($P < 0.01$) but not in diastolic ($P > 0.03$) and mean arterial blood pressure ($P > 0.1$). Minor differences in the number of reported side effects between the two treatments were not statistically significant.

Keywords pseudoephedrine hypertensive patients blood pressure nasal decongestants

Introduction

A recent review on non-prescription sympathomimetic agents (Chua & Benrimoj, 1988) suggested that pseudoephedrine may be the sympathomimetic agent with the lowest probability of causing elevation in blood pressure (BP). Studies on the pressor effect of pseudoephedrine have been undertaken predominantly in normotensive subjects except for a study by Greening (1969) in hypertensives which was not placebo-controlled.

Several authors have cautioned against the use of pseudoephedrine in hypertensive patients and suggested possible interactions with antihypertensive agents (Boyd, 1986; Precup, 1988; Saunders & Elliott, 1987). These statements are probably based on the assumption that since pseudoephedrine is an isomer of ephedrine, it has similar pharmacological properties. However, stereoisomers exhibit different pharmacological activities both quantitatively and qualitatively. The primary aim of the present study was to investigate the cardiovascular effects of single oral doses of pseudoephedrine 60 mg in hypertensive patients.

Methods

A double-blind, placebo-controlled, randomised, crossover design was used. Patients were given two capsules of either pseudoephedrine 30 mg or lactose placebo with an intervening washout period of at least 2 weeks.

Subjects

Fifteen male and five female hypertensive patients from the Endocrine-Hypertension clinic of Greenslopes Hospital, gave their written consent and approval was also obtained from the Ethics Committees of the hospital and university.

Patients were aged 31–71 (mean 51.0 ± 10.2) years and weighed 50–100 kg (mean 76.5 ± 12.3 kg). Alcohol was avoided for at least 12 h, caffeine-containing food or drinks for 3 h, and a similar type of breakfast or lunch was taken at least 2 h prior to each study visit.

The BP of nine patients was controlled with low salt diet alone, four with antihypertensive agents and seven with both types of therapy. Antihypertensive agents remained constant throughout the study period. Fifteen of the

patients were also on other medications and seven had other diseases which were not expected to interfere with the pressor effects of pseudoephedrine.

Materials

Test materials were prepared by Reckitt & Colman Pharmaceutical Co.:
(a) lactose B.P. 1980 (placebo) filled in size 1, red, opaque capsules, and
(b) S(+)-pseudoephedrine 30 mg (from half a tablet of Sudafed®) filled in capsules identical to that of placebo.

Protocol

The time of the day and study environment were the same for both treatments in each patient. After the patient had rested for at least 5 min, baseline readings, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and heart rate (HR), were taken every 5 min for 30 min. Treatment was administered with about 50 ml of water and further measurements taken for another 210 min. The means of the seven values immediately prior to treatment were considered as the mean baseline values. BP was measured with an automatic indirect BP recorder (DINAMAP™), on the same arm in both treatments and with the patient in the semi-recumbent position.

At the end of each study period, patients were questioned with a prompt list as to any side effects. On completion of both treatments, patients' opinions on which could be the active treatment were recorded.

Statistical analysis

The mean baseline values on placebo and pseudoephedrine treatment days were compared using a two-tailed paired *t*-test. The 42 points obtained after treatment were subtracted individually from the mean baseline values of each patient. The means of the 42 changes for each patient were considered as the dependent variables in the analysis of variance (ANOVA), while the independent variables consisted of treatment effects, interpatient variations and the order of treatment.

Side effects indicated by the patients during placebo and pseudoephedrine treatments were compared using McNemar's test (Armitage & Berry, 1987) and Wilcoxon signed rank sum test (Mosteller & Rourke, 1973).

Results

Both SBP and DBP appeared to increase over the period of recording (Figure 1). The mean baseline values on placebo and pseudoephedrine treatment days showed no significant difference ($P > 0.4$). After treatment, significant differences between pseudoephedrine and placebo were observed for changes in SBP ($P < 0.03$) and HR ($P < 0.01$) but not in DBP ($P > 0.3$) and MAP ($P > 0.1$) (Table 1).

Side effects reported for the two treatments were not statistically significant ($P > 0.2$). Dry mouth was the most common side effect, followed by lethargy, drowsiness and headache. Nine of the 13 patients (69.2%) who were questioned as to any difference between the two treatments, felt that both treatments were the same. Two patients thought that placebo was the active treatment while another two patients indicated pseudoephedrine.

Discussion

The mean changes from baseline for each patient was used as the dependent variable in the statistical analysis instead of the peak changes in order to avoid usage of peak values which might be due to environmental or emotional stimuli. Changes from baseline were used instead of absolute levels to eliminate day to day variations. Increases in BP over the period of recording or circadian variations were nullified by comparing the data from pseudoephedrine with that from placebo treatment, obtained at an identical time of the day. Statistically significantly greater increases in SBP were observed with pseudoephedrine than placebo treatment. The reduction in HR over time was significantly attenuated by pseudoephedrine treatment.

Single doses of pseudoephedrine 60 mg had a pronounced effect on HR in hypertensive patients unlike studies in normotensive subjects which did not show any significant effect on HR (Bye *et al.*, 1974; Empey *et al.*, 1980). This could be attributed to a reduction in the sensitivity of the compensatory baroreflex mechanisms in hypertensive patients (Bristow *et al.*, 1969; Gribbin *et al.*, 1971). In normotensive subjects, reflex bradycardia usually accompanied BP elevation. This probably attenuated the β_1-cardiostimulatory activities of pseudoephedrine and consequently its pressor effects.

In conclusion, single doses of pseudoephedrine 60 mg did not produce clinical symptoms but statistically significant effects on SBP and HR were observed.

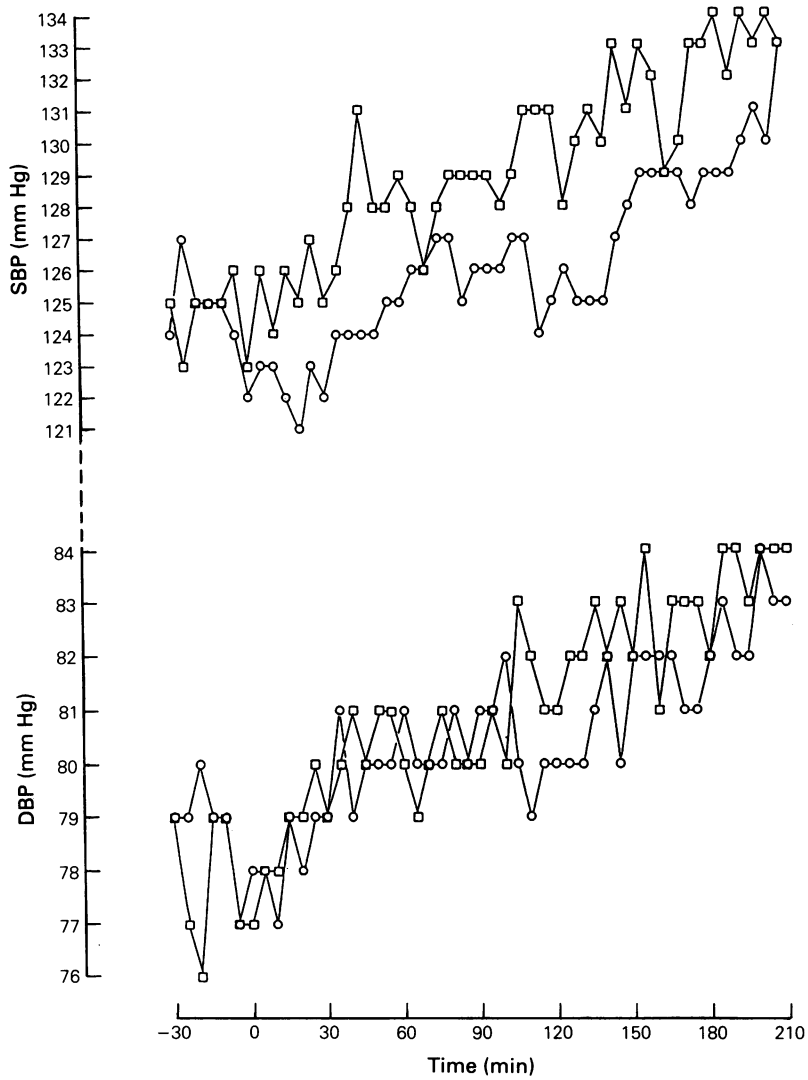

Figure 1 Mean profile (n = 20) for systolic (SBP) and diastolic blood pressure (DBP) following placebo (○) and pseudoephedrine 60 mg (□). Standard deviations (s.d.) of SBP ranged from 10.5–17.4 and 8.5–15.4 mm Hg, and of DBP ranged from 10.1–14.7 and 8.6–12.1 mm Hg for placebo and pseudoephedrine, respectively.

Table 1 Statistical differences between pseudoephedrine and placebo treatments

Variables	*Means* ± s.d.*		*Mean†*	*ANOVA* F *values*			P *values*		
	Placebo	*PS*	*(95% C.I.)*	*TR*	*PT*	*ORD*	*TR*	*PT*	*ORD*
SBP (mm Hg)	2.1 ± 6.0	5.0 ± 6.8	2.9 (0.5, 5.3)	6.0	4.8	1.8	0.02	0.00	0.19
DBP (mm Hg)	2.3 ± 4.7	3.3 ± 4.3	1.1 (–0.9, 3.1)	1.0	2.7	0.6	0.32	0.02	0.45
MAP (mm Hg)	2.5 ± 5.5	4.0 ± 5.7	1.5 (–0.6, 3.6)	2.0	4.6	2.4	0.17	0.00	0.14
HR (beats min^{-1})	–6.9 ± 4.7	–2.5 ± 3.5	3.4 (1.3, 5.5)	9.6	1.8	0.1	0.01	0.11	0.75

* Overall mean changes from baseline, with $n = 20$.
† Mean differences in the overall changes from baseline between placebo and pseudoephedrine treatments, with $n = 20$.
PS = pseudoephedrine, TR = treatment effects, PT = patient effects,
ORD = effects of treatment order, s.d. = standard deviation,
C.I. = confidence intervals.

The clinical trial was supported by Reckitt and Colman Pharmaceuticals. The cooperation of the patients, and assistance from Mary Ziesak (Hypertension Sister) and Dr Brenda Gueizelar (Research Assistant) are greatly appreciated.

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(Received 20 February 1989, accepted 10 May 1989)