Br. J. clin. Pharmac. (1978), **6**, 221–225

COMPARISON OF THE EFFECTS OF D-(–)-EPHEDRINE AND L-(+)-PSEUDOEPHEDRINE ON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS IN MAN

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1 In a preliminary double-blind trial the effects of ephedrine and pseudoephedrine on the blood pressure and heart rate of resting healthy volunteers were compared. Ephedrine 60 or 90 mg were required to raise the diastolic blood pressure above 90 mmHg, whereas 210 or 240 mg pseudoephedrine were required to produce the same effect.

2 In a second double-blind trial, patients with reversible airways obstruction were given 60 mg ephedrine or 210 mg pseudoephedrine and the effects on forced expiratory volume in one second (FEV_1) compared. Both isomers produced some bronchodilation, but the effect of pseudoephedrine was less than half that of ephedrine.

3 The reasons for these differences between the isomers are discussed and the efficacy of pseudoephedrine as a nasal decongestant pointed out and explained in relation to its effect on α-adrenoceptors in the nasal blood vessels.

Introduction

Ephedrine and pseudoephedrine are known to increase blood pressure in animals (Patil, Tye & Lapidus, 1965) and man. Elevations of systolic blood pressure after pseudoephedrine administration were reported in nine subjects by Chen (1927), the rise being smaller and of shorter duration than after administration of ephedrine. Dimson (1934) gave ephedrine and pseudoephedrine subcutaneously to patients whose conditions included carcinoma, moderate hypertension and Addisons disease, and concluded that pseudoephedrine had half the pressor effect of ephedrine. In normal healthy volunteers Bye, Dewsbury & Peck (1974) showed that ephedrine is four times as potent as pseudoephedrine in raising the systolic blood pressure.

The comparative bronchodilator effects of the two isomers have been less well documented (British Medical Journal, 1931). Levy, Permutt & Russell (1961) compared the effects of intravenous administration of pseudoephedrine with aminophylline in patients who had suffered recent attacks of acute airways obstruction and found 200 mg pseudoephedrine to have no effect on FEV_1 or forced vital capacity (FVC) when compared with placebo. Oral administration of 180 mg pseudoephedrine to ten patients with 'bronchial obstructive disease' showed a moderate but biologically significant activity (Silver & Okasaki, 1963). It thus appeared that pseudoephedrine might have relatively little action on the cardiovascular system as compared with ephedrine, but could possibly possess some useful bronchodilator activity.

The main purpose of the present study was to compare the bronchodilator activity of ephedrine and pseudoephedrine. It was decided to carry out preliminary dose-response studies to determine doses having approximately equiactive pressor effects. We deliberately chose doses that were likely to produce definite changes in blood pressure. We elected to carry out this study in healthy young volunteers without any evidence of cardiac disease and who were not receiving any regular β-adrenergic receptor stimulants. We took a diastolic blood pressure of 90 mmHg as being the pressor end point, since this would have *clinical* significance in such subjects. The equipotent doses determined in this volunteer study were used for the second study carried out in patients.

Methods

a) Four healthy volunteers (see Table 1) gave informed consent to the trial and were studied while lying supine attached to an electrocardiograph. A continuous record of the electrocardiogram was displayed on an oscilloscope and heart rate was measured at intervals by taking a half-minute recording of the ECG on paper strip and counting the R waves. Blood pressure

was taken manually using a sphygmomanometer. Five measurements of heart rate and blood pressure were made during the 15 min before administration of the drugs to obtain base line values (Figure 1). Thereafter similar measurements were made at 10 min intervals during the next 4 h.

Identical capsules were prepared containing lactose placebo, doses of 30, 60 and 90 mg ephedrine, and 60, 90, 120, 150, 180, 210 and 240 mg pseudoephedrine hydrochloride. These were administered in a random, double-blind manner. All the subjects took all the dose levels of each drug and placebo. A single treatment was administered on each occasion and studies were performed at least 2 days apart and at the same time of day.

b) Six men and three women, whose ages ranged from 36–69 years, suffering from reversible airways obstruction were studied. All of them improved their FEV_1 by 15% or more following administration of a bronchodilator aerosol. All had a clinical diagnosis of bronchial asthma, though some had an additional element of bronchitis. Bronchodilators were discontinued for 24 h before each study. Two subjects who had received the same dose of steroids during the preceding 3 months were included in the trial and continued with their regular dosage throughout.

For the bronchodilation study, identical capsules containing lactose placebo, 60 mg ephedrine and 210 mg pseudoephedrine were prepared. The nine subjects were each studied in a group on three occasions 1 week apart. Treatments were allocated by the trial co-ordinator in such a way that on each occasion three subjects received each of the three treatments. The trial was again double-blind as far as the patients and the observer making the measurements were concerned.

Three Vitalograph dry spirometers (Drew & Hughes, 1969) were assigned to the same groups of three subjects on each occasion. Studies were performed at the same time of day and each member of the group used the instrument in the same order. One hour after a light breakfast an initial set of readings was obtained for all subjects before they took their capsule. Thereafter three successive vital capacity and FEV_1 readings were recorded for each subject every 15 min for 4 h. Increase in FEV_1 was used as the index of improvement of airways obstruction. At the end of the third day each subject inhaled three doses of orciprenaline aerosol, and after 3 min a final set of readings was obtained.

Results

(a) *Preliminary cardiovascular study*

Table 1 shows the lowest doses of ephedrine and pseudoephedrine to produce a diastolic pressure of 90 mmHg, or above. The corresponding mean systolic pressures for a mean dose of 75 mg ephedrine and 232.5 mg pseudoephedrine were 171 and 155 mmHg, respectively. Changes in pulse rate were small, particularly after pseudoephedrine. The highest pulse rate recorded was 84 beats/min after 240 mg pseudoephedrine in a subject whose basal value was 74 beats/min. Even following ephedrine changes were not usually great in our fit young subjects, the biggest change being from 76–84 beats/min after 90 mg. No changes in the electrocardiogram other than those from increased rate were found in any subject receiving any dose of drug.

More typical changes were those illustrated in Figure 1 showing the changes in blood pressure and pulse rate in subject no. 2 after 240 mg pseudoephedrine.

The number of subjects studied was felt to be too small to apply extensive statistical analysis to the changes in pulse rate or systolic or diastolic pressure. It appeared that ephedrine was about 3.5 times more potent than pseudoephedrine in raising the diastolic pressure and perhaps 4 times more potent in raising the systolic. A dose of 210 mg pseudoephedrine was therefore decided upon for the trial in patients with airways obstruction.

Table 1 Lowest oral doses of ephedrine and pseudoephedrine producing elevation of diastolic blood pressure up to or above 90 mmHg in four normal subjects

			Ephedrine			*Pseudoephedrine*			*Placebo*	
Subject (Sex)	*Age (years)*	*Weight (kg)*	*Dose (mg)*	*Dose (mg/kg)*	*Diastolic BP (mmHg)*	*Dose (mg)*	*Dose (mg/kg)*	*Diastolic BP (mmHg)*	*Resting diastolic BP (mmHg)*	*Highest diastolic BP (mmHg)*
1 (M)	20	68.5	60	0.875	100	210	3.05	100	75	80
2 (F)	20	75	90	1.2	110	240	3.2	100	80	85
3 (F)	19	60	90	1.5	95	240	4.0	100	70	70
4 (M)	21	75	60	0.8	90	240	3.2	90	75	80
Mean	20	69.6	75	1.08	98.8	232.5	3.34	97.5	75	78.8

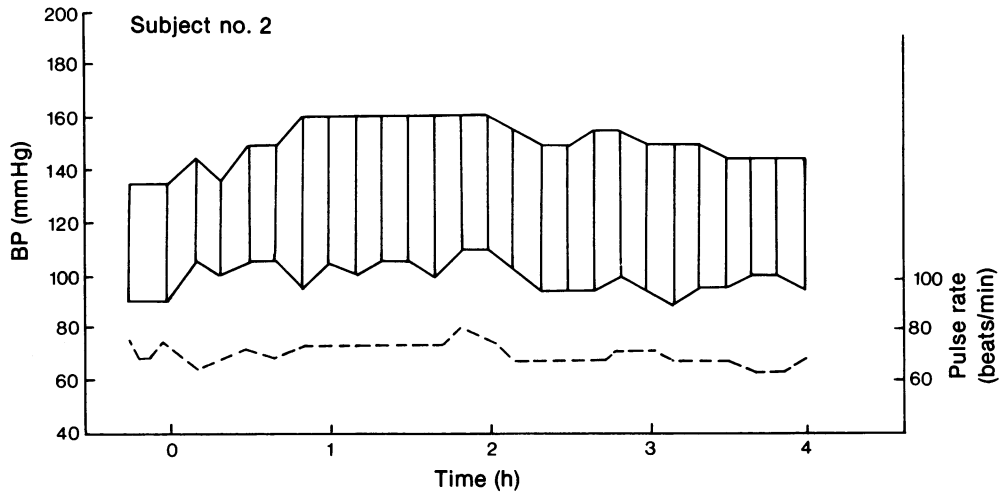

Figure 1 Changes in blood pressure (mmHg) and pulse rate (beats/min) in subject no. 2 following 240 mg pseudoephedrine.

(b) *Study of airways resistance*

Subjects made three attempts at each time of observation and statistical analysis was applied after selection of the best FEV_1. With this variable, the values of times following treatment were expressed as the percentage change from the value at zero time. Analysis of the data was made at each time of observation to determine the percentage change following administration of the treatments. The mean percentage changes of the groups are shown in Figure 2. There was no statistically significant difference between the starting values of FEV_1 on the three different occasions.

The results of an analysis of variance on the data averaged overall post-drug times, are shown in Table 2, from which it will be seen that the differences in treatment means are very significant ($P<0.01$). A multiple range test (Harter, 1959) indicates that ephedrine differs significantly from placebo and pseudoephedrine but that these last two, placebo and pseudoephedrine, do not differ significantly from each other ($P>0.05$).

It is arguable that subjects with a lesser degree of pulmonary impairment may be capable of a smaller increase in the mean percentage change in FEV_1 than subjects with a greater degree of impairment. This hypothesis was tested by computing the correlation

Table 2 Analysis of variance of mean percentage change in FEV_1 for subjects and treatments

	Treatment			
	Pseudoephedrine	*Placebo*	*Ephedrine*	*Means all treatments*
% change in FEV_1 mean all subjects	6.45	−3.14	17.74	7.02

Source of variation	*Degrees of freedom*	*Sum of squares*	*Mean squares*	F
Treatments	2	1966.7786	983.389	9.1027**
Subjects	8	1977.4471	247.1810	2.2880†
Error	16	1728.5099	108.0318	
Total	26	5672.7356		

** $0.01>P>0.001$
† $0.10>P>0.05$

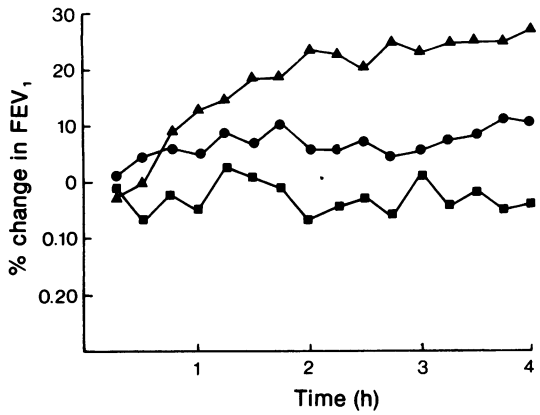

Figure 2 Mean change in FEV_1 in nine asthmatic subjects after 60 mg ephedrine (▲), 210 mg pseudoephedrine (●) and placebo (■).

between zero time FEV_1 and the average percentage change in FEV_1 at all times following treatment after removing the effects of subjects and treatments. The correlation coefficient was found to be –0.7848 which is highly significant ($P<0.01$). Using the regression obtained from this analysis the percentage change of FEV_1, corrected for different zero time FEV (X_1) and evaluated at the overall mean zero time FEV_1 is as follows:

$$X_1 = X + 51.3244\,(Y - 1.3756)$$

where X = the observed (uncorrected) change in FEV_1 and Y = the observed zero time FEV_1.

Applying such a correction to the treatment means shown in Table 2 leads to the analysis shown in Table 3. Each of these treatment means differs significantly from any other treatment mean ($P>0.05$).

The value for the placebo treatment mean is insignificantly different from zero, the treatment means for both ephedrine and pseudoephedrine being both significantly greater than zero.

The conclusions which may be drawn from this analysis are as follows:

1. The comparison of percentage changes in FEV_1 are made more sensitive by taking account of concomitant variation in the zero time FEV_1.
2. Both ephedrine and pseudoephedrine are associated with significant improvements in the mean FEV_1 following treatment.
3. At the dose levels employed ephedrine is associated with a significantly greater improvement in the mean FEV_1 following treatment than the improvement due to pseudoephedrine.

Discussion

This study confirms previous findings that the cardiovascular effects of pseudoephedrine are considerably less than those of ephedrine. Appreciable rises in diastolic blood pressure in four normal subjects did not occur until doses of pseudoephedrine in excess of 200 mg were used (3–4 mg/kg) and the subjects received up to 240 mg without unpleasant side effects. This is in accord with the findings of Bye *et al.* (1974) who found no elevation of diastolic pressure with doses of pseudoephedrine up to 180 mg, although they recorded some small increases in systolic pressure.

Pseudoephedrine does appear to have some bronchodilator action, although even 210 mg had less effect than 60 mg of ephedrine. In other words, using doses of the two isomers with an approximately equipotent pressor effect, the bronchodilator effect of pseudoephedrine was less than half that of ephedrine. The degree of bronchodilation even with 210 mg pseudoephedrine is poor compared with current β-

Table 3 Analysis of variance of mean percentage change in FEV_1 with covariance adjustment for concomitant variation in zero time FEV_1

	Treatment		
	Pseudoephedrine	*Placebo*	*Ephedrine*
Corrected means of all subjects	6.29	–0.92	15.48

Each of these treatment means is significantly different from any other treatment mean ($P<0.05$).

Source of variation	*Degrees of freedom*	*Sum of squares*	*Mean squares*	F
Treatments	2	1158.3205	597.1512	13.0853**
Subjects	8	2840.9417	355.1177	8.0235**
Error	15	663.8908	44.2594	

** $P<0.001$

adrenergic receptor stimulants, such as salbutamol. Any further increase in the dose of pseudoephedrine, even if it improved the bronchodilator effect, may well produce increased cardiovascular effects. The doses we used were already considerably higher than the conventional ones, which are commonly 15–60 mg ephedrine and 25–60 mg pseudoephedrine (Martindale, 1972), although there is good evidence that 25 mg ephedrine produces effective bronchodilation in asthmatic children (Tinkelman & Avner, 1976).

Measurements of FEV_1 are simple and provide a recognized and well-established measure of airways obstruction. However, it has been suggested that measurements of airways resistance and of flow rates derived from flow-volume curves may be a more sensitive indication of the degree of obstruction. This point is discussed more fully elsewhere (Haydu, Empey & Hughes, 1974). Therefore, it may be worthwhile using such measurements in addition to, or instead of, FEV_1 in any further trial of pseudoephedrine, especially at a lower dose, such as 60 mg. This dose might be unlikely to have much bronchodilator action, but has been shown to be an effective nasal decongestant, both in improving maximal and inspiratory flow rate in patients suffering from vasomotor rhinitis (Benson, 1970) and during a two-week trial in allergic rhinitis where subjective symptoms were assessed (Empey, Bye, Hodder & Hughes, 1975).

In view of the diversity of action of the sympathomimetic amines, it is not surprising that ephedrine and pseudoephedrine should differ in their potency. The relative ineffectiveness of pseudoephedrine as a bronchodilator may be explained in terms of its having a less potent effect on β-adrenoceptors than ephedrine. The pressor effect of pseudoephedrine is less than ephedrine; this is probably also due to its less pronounced β-adrenoceptor stimulant action. Nasal decongestion, however, is primarily due to stimulation of α-adrenoceptors in the blood vessels of the mucous membranes, and the effect of pseudoephedrine here is equal to that of ephedrine (Aviado, 1959). It would therefore appear that pseudoephedrine has much less effect on β-adrenoceptors than ephedrine but has similar activity as far as the α-adrenoceptors in the nasal blood vessels are concerned.

The authors would like to acknowledge the assistance of Drs Judy Brown, C. Good, Hilary Haines and A. Khalili in carrying out this study.

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(Received August 16, 1977)