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Cardiovascular effects of a chlorpheniramine/paracetamol combination in hypertensive patients who were sensitive to the pressor effect of pseudoephedrine

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Twelve hypertensive patients who were classified as pseudoephedrine-sensitive in a preliminary trial were selected for further investigation with single doses of pseudoephedrine 60 mg, a combination of chlorpheniramine 4 mg with paracetamol 650 mg and placebo. A double-blind, randomised, crossover study design was followed. Treatment with pseudoephedrine produced significant effects on all the four variables measured (systolic, diastolic and mean arterial blood pressure, and heart rate). Effects of the chlorpheniramine/paracetamol combination were found to be not significantly different from placebo. It was concluded that the combination may be useful as a medication for 'colds' in hypertensive patients, since it does not induce cardiovascular effects such as those observed with pseudoephedrine.

Keywords pseudoephedrine chlorpheniramine paracetamol hypertensive patients blood pressure heart rate

Introduction

In a recent study of pseudoephedrine in hypertensive patients significant interpatient variability in pressor responses to pseudoephedrine was observed (Chua *et al.*, 1989). An alternative 'cold' medication would be preferred for these patients, and antihistamines are favoured by some clinicians.

Antihistamines do not seem to have significant effects on blood pressure (BP) at doses used in non-prescription medications (Britton *et al.*, 1978; Empey *et al.*, 1984; Food and Drug Administration, 1976). Chlorpheniramine is commonly used at a dose of 4 mg every 4 to 6 h. The inclusion of an analgesic/antipyretic agent may alleviate the symptoms of the common cold. Paracetamol is preferable to aspirin for hypertensive patients, as non-steroidal anti-inflammatory agents may raise BP or attenuate the hypotensive effect of some antihypertensive agents (Brown *et al.*, 1986; Watkins *et al.*, 1980).

The present study followed a clinical trial which identified hypertensive patients who had a pressor response to pseudoephedrine 60 mg (Chua *et al.*, 1989). The effects of an alternative 'cold' medication comprising of chlopheniramine and paracetamol were tested in these patients sensitive to the pressor effects of pseudoephedrine.

Methods

Using a double-blind, placebo-controlled, randomised, crossover design patients were given either two capsules of pseudoephedrine 30 mg, chlorpheniramine 2 mg and paracetamol 325 mg or lactose placebo. A washout period of at least 2 weeks separated each study day for each patient. The trial protocol was approved by the Ethics Committee of Greenslopes Hospital and the Ethics Review Committee, University of Queensland.

Materials

Study medication, were:
(a) (S+)-pseudoephedrine 30 mg, (half a tablet of Sudafed ™) and filled in a size 1 red, opaque capsule,
(b) Chlorpheniramine maleate 2 mg with paracetamol 325 mg (Hicold ™), in an identical capsule,
(c) Placebo: Lactose in an identical capsule.

Subjects

The subjects were patients sensitive to the pressor effect of pseudoephedrine as selected by changes in systolic BP

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in the initial study (Chua *et al.*, 1989). The patients selected were aged 31–71 and weighed 59–105 kg. Four had BP controlled by diet alone and eight were taking antihypertensive agents. Antihypertensive therapy remained constant throughout the study period and other medications were monitored for possible interactions. Patients on medications such as monoamine oxidase inhibitors or psychotropic drugs which could interact with the test medications were excluded.

Patients were requested to avoid alcohol for at least 12 h and caffeine containing food or drinks for at least 3 h prior to administration of study materials. They had a similar type of breakfast at least 2 h before treatment on each study day.

Protocol

The three treatments, pseudoephedrine 60 mg, chlorpheniramine 4 mg and paracetamol 650 mg, or placebo were administered in random order. Treatment was taken between 08.00 h–09.00 h for 10 patients and between 13.00 h–14.00 h for the other two patients. The time and study environment were constant for each patient. After the patient had rested for at least 5 min, baseline readings of systolic BP (SBP), diastolic BP (DBP), mean arterial BP (MAP) and heart rate (HR), were taken every 5 min for 30 min. The means of these seven values for each variable was taken as the baseline value. Treatments were administered with 50 ml of water of time 0, and BP and HR measured every 5 min for another 210 min. BP and HR were measured on the same arm with an automatic indirect BP recorder (Dinamap TM, vital signs monitor 1846, CRITIKON, Inc., USA). All measurements were taken in the semi-recumbent position.

Data analysis

Each patient's data consisted of 42 points after treatment (5 min intervals for 210 min). Subtracting the mean baseline values from these 42 points individually for each patient produced 42 values representing changes in each variable from baseline over time. The means of the values were considered the dependent variables. The analysis used General Linear Models (GLM) Procedure with a 'Contrast' statement in the statistical package to enable pairwise comparison among the three treatments. This procedure was used rather than of analysis of variance (ANOVA) because the treatment design was not balanced. The independent variables consisted of treatment effects and interpatient variations. The order of treatment was excluded as an independent variable from the GLM Procedure as the number of patients in each treatment order was insufficient to provide adequate degrees of freedom for this analysis.

A difference of 5 mm Hg between the test medications and placebo was considered clinically important. Where no significant difference in BP was observed between test medications and placebo the power to detect this difference was computed by the formula suggested by Bolton (1984) and Lachin (1981).

Results

The mean and range of the absolute values for the three treatments are shown in Table 1. Overall treatment factors and interpatient variations showed significant effects on all four independent variables (SBP, DBP, MAP, and HR) (Table 2). Analysis of treatment effect showed that pseudoephedrine produced significantly greater increases in SBP, DBP, and MAP, and less reduction in HR than placebo and chlorpheniramine/paracetamol combination treatments (Table 2).

Table 1 Absolute values (mean ± s.d., $n = 12$) after treatment with placebo (Pl), pseudoephedrine (PS) and chlorpheniramine/paracetamol (CP) combination

Variable	*Pl*	*PS*	*CP*
SBP (mm Hg)	123 ± 11	127 ± 11	121 ± 12
DBP (mm Hg)	78 ± 10	80 ± 10	76 ± 11
MAP (mm Hg)	94 ± 11	96 ± 11	92 ± 11
HR (beats min^{-1})	55 ± 7	59 ± 11	54 ± 7

Table 2 Mean ± s.d. ($n = 12$) changes from baseline for pseudoephedrine (PS), placebo (Pl) and chlorpheniramine/paracetamol (CP) combination and statistical differences between treatments

Variable	*Pl*	*PS*	*CP*	*GLM P values* *PS/Pl*	*PS/CP*	*CP/PL*
SBP (mm Hg)	2.4 ± 3.3	6.9 ± 5.9	1.2 ± 6.0	0.002 **	0.0002 **	0.346
DBP (mm Hg)	2.5 ± 3.4	4.8 ± 4.6	1.8 ± 2.9	0.016 *	0.002 **	0.456
MAP (mm Hg)	2.9 ± 3.9	6.0 ± 4.3	3.0 ± 3.3	0.003 **	0.004 **	0.941
HR (beats min^{-1})	−3.6 ± 2.9	−1.3 ± 3.3	−4.1 ± 2.8	0.001 **	0.0003 **	0.497

* Significant at $P \leq 0.05$, ** significant at $P \leq 0.01$

Chlorpheniramine/paracetamol combination treatment was not significantly different from that of the placebo.

The power to detect a 5 mm Hg difference was calculated as 90–95% at 5% level of significance. The minimum difference which could be detected with a 70% power was 3.7 mm Hg.

Discussion and Conclusions

The changes in SBP, DBP, MAP, and HR over time in pseudoephedrine-sensitive patients were similar for the chlorpheniramine/paracetamol combination and placebo treatments. This agrees with that of other studies on antihistamines (Britton *et al.*, 1978; Empey *et al.*, 1984) although these studies were on normotensive subjects and were not specifically designed to evaluate the pressor effects of antihistamines.

Single doses of pseudoephedrine 60 mg in patients who had been previously defined as sensitive to this agent produced a highly significant pressor effect, indicating repeatability of effects. Increases in SBP over time with pseudoephedrine treatment appeared greater than with chlorpheniramine/paracetamol combination or placebo treatment while decreases in HR over time appeared less. Higher increases in DBP and MAP over time with pseudoephedrine compared to that with placebo or chlorpheniramine/paracetamol combination, were apparent about 100 min after treatment.

A mean difference between pseudoephedrine and placebo treatment of 4.5 mm Hg in SBP may or may not be clinically important. However the chlorpheniramine/paracetamol combination may be safer in hypertensive patients than pseudoephedrine. Dickerson and colleagues (1978) have found that the pressor effects of pseudoephedrine in normotensive subjects decreases with multiple doses due to development of tachyphylaxis.

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