PAPERS AND ORIGINALS

Methyldopa and propranolol or practolol in moderate hypertension

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Summary

The effect of a low dose of methyldopa combined with (a) a non-selective and (b) a selective beta-adrenoceptor antagonist was studied in a double-blind crossover trial in 24 carefully selected patients with moderate hypertension (mean initial lying blood pressure 189/117 mm Hg). Each patient received methyldopa 750 mg/day, propranolol 240 mg/day, practolol 600 mg/day, methyldopa 750 mg/day combined with propranolol 240 mg/day, methyldopa 750 mg/day combined with practolol 600 mg/day, and placebo for four weeks each according to a random sequence.

After four weeks of therapy the most effective treatment, methyldopa combined with propranolol, reduced lying and standing blood pressures by 36.5/21.4 mm Hg and 44.7/25 mm Hg respectively. This combination had similar effects to those of the combination of methyldopa with the cardioselective agent practolol except that it reduced lying diastolic pressure further. The combination was more effective than either treatment alone. No significant differences were found between the effects of propranolol, practolol, or methyldopa at the doses used.

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The study showed that the combination of a low dose of methyldopa with a non-selective or a cardioselective beta-blocker is useful and well tolerated in reducing lying, standing, and postexercise blood pressure.

Introduction

Methyldopa and beta-adrenoceptor antagonists are widely used for treating hypertension, both singly and in combination, but no within-patient studies have been carried out to assess the combined effect of these drugs. We report the findings of a study to evaluate the effect of a low dose of methyldopa combined with fixed doses of propranolol and practolol, two beta-blocking agents with different properties, in a carefully selected group of patients with moderate hypertension.

Patients and methods

SELECTION OF PATIENTS

Patients aged 21-65 years, who had been referred for investigation of raised blood pressures were assessed in hospital after at least 14 days off any drug treatment. During a 36-48 hour hospital admission routine investigations were performed, including haematology, bacteriology, biochemistry, chest x-ray examination, intravenous pyelography, and electrocardiography. Patients were excluded if there was a history of recent myocardial infarction, evidence of cardiac failure, heart block, or gross ischaemia, grade III or IV retinopathy, diabetes mellitus, gout, impaired liver function, or creatinine clearance less than 60 ml/min or if they were on any other drug treatment. Lying and standing blood pressures were recorded every four hours. The observers in the trial (DBG or JCP) also measured the blood pressures with Hawksley random-zero sphygmomanometers¹ on two separate occasions: on the evening of admission (2000-2100) and after a 10-hour overnight rest (0800-0900). On both occasions the number of 30-cm steps required to produce an increment of standing pulse of 30 beats/minute was determined using electrocardiographic control. Patients were invited to participate in the trial if the morning lying diastolic pressures (DBG or JCP) were over 105 mm Hg and under 125 mm Hg and all other outpatient and ward blood pressures

confirmed persistently raised blood pressure levels. The nature of the trial was explained and all suitable patients gave their consent.

CONDUCT OF TRIAL

After discharge from hospital the patients were seen at the hypertension clinic within two weeks. A double-blind crossover method was used to assess the effects on lying, standing, and postexercise blood pressure of six treatments, each given three times a day: (a) methyldopa 250 mg and practolol 200 mg; (b) practolol 200 mg and placebo 2; (c) propranolol 80 mg and methyldopa 250 mg; (d) propranolol 80 mg and placebo 2; (e) placebo 1 and methyldopa 250 mg; (f) placebo 1 and placebo 2.

Each treatment was given for four weeks, and each of 24 patients received the six treatments. The experimental design consisted of four 6 × 6 Latin squares chosen in such a way that each treatment period followed or preceded any other treatment period on four occasions. The drug supplies for each patient were pre-packed (in duplicate) and new containers were issued at the start of each new treatment period. Practolol, propranolol, and matching placebo were supplied by ICI Limited and methyldopa and matching placebo 2 by Merck Sharp and Dohme Limited. The "double-placebo" technique ensured that patients took the same number of tablets throughout the trial. Reserve packs were made up so that the sequence of treatments for any patient who was withdrawn from the trial were available for a substitute.

The patients were seen every two weeks and blood pressure was recorded using a Hawksley random-zero sphygmomanometer under standard conditions at the same time of day by the same observer (DBG or JCP) except on a few occasions when a deputy substituted. The mean of two or three blood pressure readings (same arm) after three to five minutes lying and after two to three minutes standing was recorded. A single reading was taken after performance of the predetermined exercise load specified for each patient. The diastolic end point was taken as the phase-4 muffle. Between-observer comparisons of the blood pressure readings were made at intervals throughout the trial.

The observer not recording the blood pressure completed a questionnaire on symptoms in another room. Separate forms were completed for every patient at each of the 12 visits. Questions included volunteered information and included specific items about general wellbeing, dizziness, headache, energy, tiredness, mood, sleep, dreams, and bowel habit. Tablet counts and body weights were recorded.

The statistical technique of analysis of variance was used to analyse the readings of blood pressure, pulse, and weight. The readings made after two weeks of each treatment were analysed separately from those made after four weeks of treatment. The analysis of variance model allowed for patient effects, treatment effects, and sequence effects. Overall assessments of the presence or absence of treatment effects were made with the F-test, and individual comparisons were carried out with Student's *t* test. Standard errors were based on the residual mean square from the analysis of variance.

Results

A complete set of observations was available for each of the 24 patients (13 men) aged 24-61 years (mean 48.5 years). Two of the

original patients were withdrawn from the study while on active treatment because of non-fatal cardiovascular "events" (cerebral thrombosis, myocardial infarction). A third patient withdrew because of domestic circumstances. Reserve duplicate drug supplies were used for their substitutes to maintain the balanced design of the trial. Tablet counts were satisfactory throughout (>90%).

The overall tests of significance showed that highly significant differences existed between treatments in terms of their effect on blood pressure and pulse after both a fortnight and one month on treatment ($P < 0.001$ in all cases). The treatment means of blood pressure, pulse, and weight are shown in table I. The effects on blood pressure and pulse are also shown in figs 1 and 2. The mean lying and standing

FIG 1—Mean blood pressures during treatment. $\triangle$ = Placebo. $\square$ = Methyldopa 750 mg/day. $\circ$ = Propranolol 240 mg/day. $\bullet$ = Practolol 600 mg/day. $\blacktriangle$ = Methyldopa 750 mg/day and propranolol 240 mg/day. $\blacksquare$ = Methyldopa 750 mg/day and practolol 600 mg/day.

blood pressures on entry to the study were 189/117 and 183/123 mm Hg. The mean values on placebo were similar to the mean initial values. The most effective treatment (methyldopa with propranolol) led to a reduction in lying and standing pressures of 36.5/21.4 mm Hg and 44.7/25 mm Hg respectively. The statistical comparison of treatments is summarised in table II. After four weeks' treatment both beta-blockers and methyldopa had highly significant effects on blood pressure and pulse rate. No significant differences were evident between the effects of propranolol, practolol, or methyldopa on blood pressure at the doses used, the reduction in lying blood pressures being about 23/12 mm Hg. The combination of methyldopa with propranolol had

TABLE I—Mean blood pressure, pulse rate, and weight in 24 patients

														Initial values	Methyldopa		Propranolol		Practolol		Methyldopa and propranolol		Methyldopa and practolol		Placebo		
															2 Weeks	4 Weeks	2 Weeks	4 Weeks	2 Weeks	4 Weeks	2 Weeks	4 Weeks	2 Weeks	4 Weeks	2 Weeks	4 Weeks	
															Blood pressure (mm Hg)												
Lying systolic	..	..	..	..	..	189.2	169.5	166.4	163.9	165.7	163.6	164.4	153.6	152.7	157.6	160.6	182.9	182.5									
Lying diastolic	..	..	..	..	..	116.9	106.2	104.7	103.3	104.9	105.3	102.8	94.3	95.5	98.3	102.2	114.5	113.7									
Standing systolic	..	..	..	..	..	182.9	156.1	159.1	162.5	158.7	159.0	154.0	142.0	138.2	136.6	147.0	172.7	175.2									
Standing diastolic	..	..	..	..	..	123.3	109.6	111.2	112.5	109.8	111.5	108.2	97.3	98.3	97.0	102.3	118.0	122.1									
Postexercise systolic	..	..	..	..	..	198.4	165.9	169.0	172.3	165.1	164.4	161.7	143.4	145.5	139.7	147.7	187.6	195.9									
Postexercise diastolic	..	..	..	..	..	119.3	104.6	103.2	107.1	106.0	104.5	102.8	92.7	93.4	90.9	98.5	112.3	116.1									
															Pulse rate (beats/min)												
Lying	..	..	..	..	..	82.1	78.0	76.4	62.4	66.3	72.3	74.0	65.7	64.7	72.3	72.6	79.9	83.5									
Standing	..	..	..	..	..	93.1	87.7	84.7	67.8	72.7	78.8	79.7	69.7	70.4	79.5	79.9	91.9	93.7									
Postexercise	..	..	..	..	..	118.3	108.0	108.4	87.0	91.4	94.5	94.7	84.5	85.3	94.4	93.4	116.8	120.0									
															Weight (kg)												
															74.9	75.8	75.2	74.5	74.2	73.8	73.8	74.9	75.0	74.9	74.9	74.6	74.2

Standard error values are available on request to the authors.

TABLE II—Comparison of treatments (P values) after four weeks of treatment in 24 patients

Comparison of treatments		Lying			Standing			Postexercise		
		Systolic BP	Diastolic BP	Pulse	Systolic BP	Diastolic BP	Pulse	Systolic BP	Diastolic BP	Pulse
Propranolol	v practolol	NS	NS	<0.001	NS	NS	<0.01	NS	NS	NS
	v methyldopa	NS	NS	<0.001	NS	NS	<0.001	NS	NS	<0.001
	v propranolol and methyldopa	<0.01	<0.001	NS	<0.001	<0.001	NS	<0.001	<0.001	NS
	v practolol and methyldopa	NS	NS	<0.01	<0.01	<0.001	<0.01	<0.001	<0.02	NS
Methyldopa	v practolol	NS	NS	NS	NS	NS	<0.05	NS	NS	<0.001
	v propranolol and methyldopa	<0.01	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.001
	v practolol and methyldopa	NS	NS	NS	<0.01	<0.001	<0.05	<0.001	NS	<0.001
Practolol	v propranolol and methyldopa	<0.01	<0.01	<0.001	<0.001	<0.001	<0.001	<0.01	<0.01	<0.01
	v practolol and methyldopa	NS	NS	<0.01	NS	<0.05	NS	<0.01	NS	NS
Propranolol and methyldopa v practolol and methyldopa		NS	<0.02	<0.001	NS	NS	<0.001	NS	NS	<0.02
Methyldopa v placebo		<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Propranolol v placebo		<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

BP = Blood pressure. NS = Not significant.

a significantly greater effect on lying diastolic pressure than did that with practolol, but this difference was not seen in other positions. The combination of methyldopa and propranolol was significantly more effective than either treatment alone. The lying and standing pulse rates were higher on treatment with practolol, which has intrinsic sympathomimetic activity, than on propranolol, which does not have this property. Mean weight was significantly higher ($P < 0.001$) when patients were on methyldopa. No evidence of a pressor effect was detected in any patient during treatment with the combination of methyldopa and propranolol.

FIG 2—Mean pulse rates during treatment. See legend to figure 1 for key to treatments.

Detailed analysis of the questionnaires on side effects showed that all treatments (including placebo) were associated with similar side effects.

Discussion

Our results in this within-patient crossover study show that in a group of carefully selected patients with moderate hypertension the individual drugs at the fixed doses chosen had a similar effect on blood pressure. The effect of methyldopa combined with propranolol or practolol was similar and usually greater than that of the drugs given alone. The combined effect seemed to be additive without evidence of potentiation or antagonism.

The study allowed within-patient comparisons of the individual treatments, and placebo, but the complexity of the balanced sequence of treatments in the design in a group of patients with resting diastolic blood pressures of approximately 120 mm Hg (phase-4) imposed certain restrictions on the conduct of the study. For example, we thought that patients

should not be exposed to longer than a six-month trial, one month of which would be on placebo, as the adequacy of treatment during the different treatment periods could not be predicted. Secondly, one month on each treatment was chosen to allow adequate time for the effects to become evident and for the influence of any carry-over effects to be minimised. A variable dose study for each beta-blocker would have added to the interest of the study but in such a complex design this would have been unworkable and would have doubled or trebled the duration of the observations far beyond the three years that the study took to complete.

The doses of the beta-blockers were chosen on the basis of dose-finding studies by the manufacturers at the time the trial was designed. The effect of an untreated patient entering the study and being treated immediately with combined treatment—for example, methyldopa 750 mg with propranolol 240 mg/day—or suddenly switching to placebo therapy also had to be considered. The dose of methyldopa chosen was low; this was deliberate as the principal aim of the study was to assess the combined effect of a low dose of this drug with beta-blocking agents with differing properties. We accept that a larger dose of methyldopa might have resulted in an increased hypotensive effect but this was not the aim of the study. Practolol is much less lipid-soluble than propranolol, but despite this property, and the possession of partial agonist activity and a selective action on β_1 -adrenoceptors, its effects, at least at the arbitrary doses used, were similar to those of propranolol either alone or in combination with methyldopa. The major clinical advantage of both beta-blockers and methyldopa is their ability to lower supine blood pressure, alone or in combination. Further studies are required to evaluate the comparative merits of combined treatment with beta-blockers, selective and non-selective, and other agents such as adrenergic neurone blockers and clonidine. The recent report on the effects of combined treatment with guanethidine and oxprenolol suggests that this combination is also of value,² but direct comparisons with our study cannot be made. We conclude that the combination of a low dose of methyldopa with propranolol or with a cardioselective beta-blocker such as practolol is useful in reducing lying, standing, and post-exercise blood pressure levels. The combination is well tolerated in the management of moderate hypertension.

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References

¹ Wright, B M, and Dore, C F, *Lancet*, 1970, **1**, 337.
² Pearson, R M, *et al*, *British Medical Journal*, 1976, **1**, 933.