CARDIOVASCULAR EFFECTS OF ALINIDINE AND PROPRANOLOL ALONE AND IN COMBINATION WITH HYDRALAZINE IN NORMAL MAN

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1 The effect of single oral doses of alinidine 80 mg, propranolol 40 mg, hydralazine 50 mg, alinidine 80 mg combined with hydralazine 50 mg, propranolol 40 mg combined with hydralazine 50 mg, and placebo on arterial pressure and heart rate was studied in five normal volunteers in the supine and standing positions and during exercise. Observations were made before and at 1, 2, 3, 4 and 6 h after drug administration.

2 Alinidine 80 mg and propranolol 40 mg significantly reduced heart rate in the supine position, and on exercise. The reductions in supine heart rate produced by alinidine and propranolol were not significantly different, but the maximum effect of alinidine on exercise heart rate was observed later than that of propranolol. Propranolol reduced heart rate in the standing position at all time intervals after drug administration, but alinidine reduced standing heart rate only at 6 h ($P < 0.01$ when compared to placebo).

3 Hydralazine 50 mg increased supine heart rate by 8–10 beats min^{-1} when compared to the pre-treatment value. These increases were significant ($P < 0.05$) when compared to the pre-treatment value, but not when compared to placebo. Hydralazine increased standing heart rate from 71.4 ± 6.5 to 90.0 ± 7.0 beats min^{-1} ($P < 0.05$ when compared to placebo), but had no effect on exercise heart rate. The small increase in supine heart rate following hydralazine therapy was reduced by alinidine and propranolol, but only propranolol reduced the significant increase in standing heart rate produced by hydralazine.

4 Hydralazine reduced diastolic arterial pressure in the supine position at 2 and 4 h after drug administration ($P < 0.05$ when compared to placebo), but had no effect on systolic or diastolic arterial pressure in the standing position or on exercise.

5 Propranolol produced small reductions in systolic arterial pressure in the standing position, which were not significant when compared to placebo; diastolic pressure was unchanged. Propranolol reduced systolic pressure during exercise at 2, 4 and 6 h after drug administration ($P < 0.05$ when compared to placebo); diastolic pressure was unchanged. The effects of hydralazine and propranolol combined on arterial pressure in the standing position were similar to those observed after propranolol alone, but combined therapy produced a greater reduction in exercise systolic pressure, although these differences were not significant.

6 Alinidine reduced systolic arterial pressure in the supine position at 3, 4 and 6 h after drug administration ($P < 0.01$) and diastolic pressure at 2 and 4 h ($P < 0.05$ when compared to placebo). Alinidine reduced systolic arterial pressure in the standing position at 3, 4 and 6 h after drug administration ($P < 0.05$) and diastolic pressure at 2 h ($P < 0.01$) and 6 h ($P < 0.05$ when compared to placebo). During exercise, alinidine produced a small reduction in systolic arterial pressure which was not significant, and a reduction in diastolic pressure at 1 h ($P < 0.05$ when compared to placebo). The effects of hydralazine and alinidine combined on arterial pressure were similar to those observed after alinidine alone.

7 Hydralazine and alinidine combined produced a greater fall in systolic arterial pressure in the standing position than the changes observed after hydralazine alone; these differences were significant ($P < 0.05$) at 2, 3, 4 and 6 h after drug administration. However, the increase in heart rate after combined therapy was less than that observed after hydralazine alone, but these differences were not significant. This would suggest that alinidine may reduce the tachycardia produced by hydralazine.

8 Combined therapy with hydralazine and alinidine was associated with a high incidence of side effects. Alinidine alone produced dry mouth and tiredness in some subjects and syncope in one.

- 9 Alinidine reduced heart rate and arterial pressure in normal man, and may therefore have a role in the treatment of hypertension, when used alone or in combination with vasodilator therapy.

Introduction

Hydralazine produces a tachycardia in man (Freis & Finnerty, 1950) which is thought to arise from increased sympathetic activity due to baroreceptor stimulation (Koch-Weser, 1976). The addition of propranolol to hydralazine therapy reduces the tachycardia, and the hypotensive effect of combined propranolol and hydralazine therapy is greater than with either drug alone (Zacest *et al.*, 1972).

Alinidine (*N*-allyl-clonidine) produces a sinus bradycardia in experimental animals which is unaffected by pre-treatment with atropine or phentolamine (Kobinger *et al.*, 1979a, b). Alinidine may act directly on the sinus node to restrict the flow of current through anion selective channels, thus slowing diastolic depolarisation and causing bradycardia (Millar & Vaughan-Williams, 1981). Alinidine does not inhibit an isoprenaline tachycardia in animals (Kobinger *et al.*, 1979a) or man (Harron *et al.*, 1981), but reduces an exercise tachycardia in man in a dose-dependent manner. The effect of alinidine 80 mg on an exercise tachycardia is equivalent to propranolol 40 mg (Harron *et al.*, 1981). If alinidine prevented the tachycardia produced by hydralazine, it may have a role, in place of β -adrenoceptor blocking drugs, in the treatment of hypertension in combination with hydralazine. In the present study we have compared the effects of alinidine and propranolol on the heart rate response to hydralazine therapy in normal man.

Methods

The comparative cardiovascular effects of the oral administration of alinidine 80 mg, propranolol 40 mg, hydralazine 50 mg, alinidine 80 mg combined with hydralazine 50 mg, propranolol 40 mg combined with hydralazine 50 mg and placebo were investigated in 5 healthy male volunteers aged 23 to 27 years, weight 67.5 ± 3.8 kg (mean $\pm$ s.e. mean). A further subject commenced the study, but was withdrawn due to adverse effects. The data from this subject are not included in the analysis of results. The protocol of the study had been approved by the Ethical Committee of The Queen's University of Belfast, and the subjects gave written consent to the procedure, which had been explained to them. Each subject had a normal haematological and biochemical profile prior to the study. Three subjects were slow and two subjects were fast acetylators.

Observations were made before and at 1, 2, 3, 4 and 6 h after drug administration. At each observation time the volunteers were supine for 15 min, standing

erect for 3 min, and then performed strenuous exercise by stepping on and off a box 46 cm high at a rate of 32 steps/min for 3 min. Heart rate and arterial pressure were measured at the end of the supine and erect periods. Arterial pressure was measured during the last 30 s of the exercise period, and heart rate within 5 sec of completing exercise. Heart rate was measured from lead I of a direct reading electrocardiogram, and arterial pressure was measured using a Hawksley random-zero sphygmomanometer (Wright & Dore, 1970).

Results are expressed as the mean $\pm$ s.e. mean. Statistical analyses were carried out using analysis of variance, and Duncan's multiple range test to establish significance. A *P* value of less than 0.05 was regarded as an indication of significance. The effects of active drug were compared at each time interval with the values obtained after placebo, and with the pre-treatment values.

Results

Supine position

Systolic arterial pressure was significantly increased ($P < 0.05$) at 3 h after placebo administration, when compared to the pre-treatment value, and diastolic pressure at 2 and 4 h (Table 1). Hydralazine 50 mg reduced systolic arterial pressure at 3 h, and diastolic pressure at 2 and 4 h after drug administration; these differences were significant ($P < 0.05$) when compared to placebo, but not when compared to the pre-treatment values. Alinidine 80 mg reduced systolic arterial pressure at 3, 4 and 6 h; these differences were significant ($P < 0.01$) when compared to placebo, and also when compared to the pre-treatment values ($P < 0.05$, 3 h; $P < 0.01$, 4 and 6 h). Significant reductions in diastolic pressure also occurred at 2 h ($P < 0.05$ when compared to placebo), 4 h ($P < 0.05$ when compared to placebo and to the pre-treatment value) and at 6 h ($P < 0.05$ when compared to the pre-treatment value). Propranolol 40 mg reduced systolic pressure at 3 h ($P < 0.01$ when compared to placebo, but not when compared to the pre-treatment value); diastolic pressure was unchanged. Hydralazine and alinidine combined reduced systolic arterial pressure at 3 h ($P < 0.01$ when compared to placebo, and to the pre-treatment value) and at 4 h ($P < 0.05$ when compared to the pre-treatment value), and diastolic pressure at 4 h ($P < 0.01$ when compared to placebo). Hydralazine and propranolol combined reduced

systolic pressure at 3 h and diastolic pressure at 2 and 4 h ($P < 0.01$ when compared to placebo, but not when compared to the pre-treatment values).

Following placebo administration, there was no change in heart rate in the supine position throughout the study period (Table 2). Hydralazine increased heart rate by up to 10 beats min^{-1} at all time intervals after drug administration. These differences were significant ($P < 0.05$) when compared to the pre-treatment value, but not when compared to placebo. Alinidine reduced heart rate at 3 and 4 h ($P < 0.05$ when compared to placebo). Propranolol reduced heart rate at 1 h ($P < 0.05$ when compared to the pre-treatment value), 2 h ($P < 0.05$ when compared to placebo) and at 3 and 4 h ($P < 0.01$ when compared to placebo, and $P < 0.05$ when compared to the pre-treatment value). There were no significant differences in the heart rates observed after propranolol or alinidine. When hydralazine was given in combination with alinidine or with propranolol, the heart rates observed were not significantly different from placebo, or from the pre-treatment values.

Standing position

Following placebo, there was no change in systolic or diastolic arterial pressure throughout the treatment period (Table 3). Hydralazine 50 mg produced no change in arterial pressure. Alinidine 80 mg reduced systolic arterial pressure at 2 h ($P < 0.05$ when compared to the pre-treatment value), at 3 h ($P < 0.05$ when compared to placebo and to the pre-treatment value), at 4 h ($P < 0.05$ when compared to placebo, and $P < 0.01$ when compared to the pre-treatment value), and at 6 h ($P < 0.05$ when compared to placebo). Alinidine reduced diastolic pressure at 2 h ($P < 0.01$) and 6 h ($P < 0.05$, when compared to placebo and to the pre-treatment value) and also at 4 h ($P < 0.05$ when compared to the pre-treatment value). Propranolol 40 mg produced a small reduction in systolic pressure at 2 h, but this was not significant; diastolic pressure was unchanged. Hydralazine and alinidine combined reduced systolic pressure at 2 h ($P < 0.05$ when compared to the pre-treatment value), at 3 and 4 h ($P < 0.05$ when compared to placebo, $P < 0.01$ when compared to the pre-treatment value), and at 6 h ($P < 0.05$ when compared to placebo); diastolic pressure was reduced at 2 h ($P < 0.01$), 3 h ($P < 0.05$) and 6 h ($P < 0.01$ when compared to placebo). The reductions in systolic pressure produced by hydralazine and alinidine combined were significantly greater than the values observed after hydralazine alone at 2, 3, 4 and 6 h ($P < 0.05$). There were no significant differences between the reductions in arterial pressure produced by hydralazine and alinidine combined, and those produced by alinidine alone. Hydralazine and propranolol combined had no significant effects on systolic or diastolic pressure.

Table 1 Supine arterial pressure. Effect of placebo, hydralazine, alinidine, propranolol, the combination of hydralazine and alinidine, and the combination of hydralazine and propranolol on systolic and diastolic arterial pressure (mm Hg) in the supine position. Results are the mean ($\pm$ s.e. mean) of observation in five subjects

Treatment	Time after dosing (h)						
	0	1	2	3	4	6	
Placebo	Systolic	108.0 ± 1.8	105.0 ± 1.3	103.6 ± 4.1	117.6 ± 4.7†	106.8 ± 3.7	107.6 ± 4.7
	Diastolic	62.4 ± 2.5	62.0 ± 3.2	75.2 ± 2.8†	71.6 ± 2.8	74.8 ± 5.5†	69.6 ± 3.2
Hydralazine 50 mg	Systolic	106.0 ± 2.8	108.0 ± 4.3	104.0 ± 3.2	103.4 ± 1.9*	103.6 ± 2.9	103.6 ± 2.9
	Diastolic	63.6 ± 3.2	61.2 ± 6.6	60.8 ± 2.3*	61.4 ± 3.9	58.8 ± 3.3*	65.2 ± 3.0
Alinidine 80 mg	Systolic	108.0 ± 2.5	106.0 ± 3.3	98.8 ± 4.4	96.8 ± 4.0**†	90.0 ± 3.0**††	90.8 ± 5.0**††
	Diastolic	71.6 ± 4.6	68.8 ± 3.4	62.0 ± 1.3*	63.6 ± 0.7	59.2 ± 2.6*†	59.2 ± 1.9†
Propranolol 40 mg	Systolic	106.4 ± 4.5	100.4 ± 3.5	97.6 ± 4.3	96.8 ± 4.8**	98.4 ± 1.3	108.8 ± 3.7
	Diastolic	62.4 ± 7.7	66.0 ± 1.9	64.0 ± 1.7	62.4 ± 1.2	66.4 ± 4.3	71.6 ± 3.4
Hydralazine 50 mg	Systolic	107.6 ± 3.5	105.6 ± 2.8	106.8 ± 4.6	90.4 ± 5.2**††	94.0 ± 4.9†	105.6 ± 4.7
	Diastolic	61.2 ± 2.3	59.6 ± 1.3	67.2 ± 4.8	60.4 ± 2.2	56.8 ± 2.4**	60.4 ± 8.9
Hydralazine 50 mg	Systolic	102.4 ± 4.2	101.6 ± 3.7	99.6 ± 6.0	99.2 ± 6.0**	105.2 ± 6.5	100.8 ± 2.9
	Diastolic	64.0 ± 2.2	62.6 ± 1.7	58.4 ± 5.2**	63.6 ± 3.2	55.6 ± 4.0**	57.6 ± 6.2

* $P < 0.05$, ** $P < 0.01$ when compared to placebo; [†] $P < 0.05$, ^{††} $P < 0.01$ when compared to pre-treatment value.

Table 2 Supine heart rate. Effect of placebo, hydralazine, alinidine, propranolol, the combination of hydralazine and alinidine, and the combination of hydralazine and propranolol on heart rate (beats min⁻¹) in the supine position. Results are the mean ($\pm$ s.e. mean) of observations in five subjects

Treatment	Time after dosing (h)				
	0	1	2	3	4
Placebo	61.4 $\pm$ 5.1	58.6 $\pm$ 2.8	59.4 $\pm$ 3.6	62.4 $\pm$ 6.2	60.8 $\pm$ 3.8
Hydralazine 50 mg	54.4 $\pm$ 3.8	62.6 $\pm$ 4.8†	62.4 $\pm$ 3.5†	62.4 $\pm$ 4.5†	64.8 $\pm$ 4.6†
Alinidine 80 mg	58.0 $\pm$ 5.7	56.4 $\pm$ 4.9	56.2 $\pm$ 4.6	52.8 $\pm$ 3.2*	52.6 $\pm$ 3.5*
Propranolol 40 mg	58.8 $\pm$ 2.3	51.0 $\pm$ 3.1†	51.2 $\pm$ 2.7*	50.4 $\pm$ 3.0**†	49.4 $\pm$ 2.6**†
Hydralazine 50 mg Alinidine 80 mg	60.4 $\pm$ 2.9	63.0 $\pm$ 1.8	62.4 $\pm$ 1.7	58.8 $\pm$ 2.5	61.2 $\pm$ 2.5
Hydralazine 50 mg Propranolol 40 mg	61.8 $\pm$ 3.9	59.2 $\pm$ 4.5	59.8 $\pm$ 3.2	58.6 $\pm$ 4.9	60.0 $\pm$ 2.1

* $P < 0.05$, ** $P < 0.01$ when compared to placebo; † $P < 0.05$ when compared to the pre-treatment value.

Table 3 Standing arterial pressure. Effect of placebo, hydralazine, alinidine, propranolol, the combination of hydralazine and alinidine, and the combination of hydralazine and propranolol on systolic and diastolic arterial pressure (mm Hg) in the standing position. Results are the mean ($\pm$ s.e. mean) of observations in five subjects

Treatment	Time after dosing (h)					
	0	1	2	3	4	6
Placebo	110.8 $\pm$ 2.9	107.2 $\pm$ 2.4	103.6 $\pm$ 5.5	106.8 $\pm$ 7.3	106.0 $\pm$ 7.0	111.6 $\pm$ 1.7
Hydralazine 50 mg	78.8 $\pm$ 1.5	74.4 $\pm$ 6.9	81.6 $\pm$ 3.8	78.8 $\pm$ 2.0	74.8 $\pm$ 5.6	84.0 $\pm$ 3.7
Alinidine 80 mg	109.6 $\pm$ 3.2	112.8 $\pm$ 4.5	110.8 $\pm$ 9.1	107.6 $\pm$ 3.8	109.2 $\pm$ 2.9	110.8 $\pm$ 3.9
Propranolol 40 mg	74.4 $\pm$ 3.7	76.4 $\pm$ 2.5	74.0 $\pm$ 4.5	75.2 $\pm$ 1.4	76.0 $\pm$ 2.2	77.2 $\pm$ 3.4
Hydralazine 50 mg Alinidine 80 mg	109.6 $\pm$ 5.2	98.8 $\pm$ 5.4	92.8 $\pm$ 8.2†	93.2 $\pm$ 3.8*†	87.2 $\pm$ 3.2*††	96.8 $\pm$ 5.8*
Propranolol 40 mg	80.8 $\pm$ 2.0	68.0 $\pm$ 8.3	62.4 $\pm$ 10.3**††	69.2 $\pm$ 2.7	65.2 $\pm$ 3.9†	66.0 $\pm$ 3.3*†
Hydralazine 50 mg Alinidine 80 mg	113.8 $\pm$ 5.4	103.8 $\pm$ 3.4	99.6 $\pm$ 2.5	105.2 $\pm$ 5.5	102.2 $\pm$ 4.2	113.8 $\pm$ 7.2
Hydralazine 50 mg Propranolol 40 mg	75.4 $\pm$ 6.1	78.6 $\pm$ 3.6	71.2 $\pm$ 1.5	78.4 $\pm$ 3.7	77.8 $\pm$ 2.2	82.6 $\pm$ 4.0
Hydralazine 50 mg Alinidine 80 mg	108.8 $\pm$ 8.1	108.5 $\pm$ 5.1	94.4 $\pm$ 8.7†	88.0 $\pm$ 4.9*††	88.8 $\pm$ 4.5*††	96.4 $\pm$ 5.6*
Hydralazine 50 mg Propranolol 40 mg	66.4 $\pm$ 9.6	63.5 $\pm$ 6.6	57.6 $\pm$ 5.8**	63.2 $\pm$ 2.6*	61.6 $\pm$ 4.5	63.6 $\pm$ 2.9**
Hydralazine 50 mg Propranolol 40 mg	112.0 $\pm$ 5.2	101.2 $\pm$ 9.6	102.4 $\pm$ 6.9	100.0 $\pm$ 7.2	104.8 $\pm$ 6.7	103.6 $\pm$ 7.8
Hydralazine 50 mg Propranolol 40 mg	79.6 $\pm$ 5.3	66.4 $\pm$ 8.5	68.8 $\pm$ 6.5	68.0 $\pm$ 4.7	69.6 $\pm$ 6.8	71.2 $\pm$ 6.3

* $P < 0.05$, ** $P < 0.01$ when compared to placebo; † $P < 0.05$, †† $P < 0.01$ when compared to the pre-treatment value

Following placebo, there was no significant change in heart rate (Table 4). Following hydralazine, heart rate was increased at all time intervals. These increases were significant at 1 h ($P < 0.05$ when compared to the pre-treatment value), 2 h ($P < 0.05$ when compared to placebo, and $P < 0.01$ when compared to the pre-treatment value), 3 h ($P < 0.01$ when compared to placebo and to the pre-treatment value), and at 4 and 6 h ($P < 0.01$ when compared to the pre-treatment value). Alinidine reduced heart rate at 6 h only ($P < 0.01$ when compared to placebo). Propranolol reduced heart rate at all time intervals after drug administration. These differences were significant at 1 and 3 h ($P < 0.05$ when compared to placebo and to the pre-treatment value), 2 h ($P < 0.01$ when compared to placebo, $P < 0.05$ when compared to the pre-treatment value) 4 h ($P < 0.01$ when compared to placebo), and 6 h ($P < 0.05$ when compared to placebo). The heart rate after propranolol was significantly less ($P < 0.05$) than that observed after alinidine at 1, 2 and 3 h after drug administration. Heart rate was increased after hydralazine and alinidine combined, but this was significant only at 3 h ($P < 0.05$ when compared to placebo and to the pre-treatment value). The heart rate observed after hydralazine and alinidine combined was less than that observed after hydralazine alone, but these differences were not significant. When hydralazine was given in combination with propranolol heart rate was reduced at 1, 2 and 3 h ($P < 0.05$ when compared to the pre-treatment value). The heart rate observed after hydralazine and propranolol combined was greater than that observed after propranolol alone, but these differences were not significant. The heart rate after hydralazine and propranolol combined was less than that observed after hydralazine alone; these differences were significant ($P < 0.05$) at 1, 2, 3 and 4 h after drug administration.

Exercise

Following placebo, there was no change in systolic or diastolic arterial pressure during exercise (Table 5). Prior to drug administration, diastolic pressure varied from 48.8 ± 8.7 to 82.4 ± 5.7 mm Hg; these two values were significantly different ($P < 0.05$). Hydralazine 50 mg did not change arterial pressure. Alinidine 80 mg produced small reductions in systolic and diastolic pressure, which were not significant except for diastolic pressure at 1 h ($P < 0.05$ when compared to placebo, but not when compared to the pre-treatment value). Propranolol 40 mg produced significant reductions in systolic pressure at 1 h ($P < 0.05$ when compared to the pre-treatment value) and at 2, 4 and 6 h ($P < 0.05$ when compared to placebo and to the pre-treatment value); diastolic pressure was unchanged. Hydralazine and alinidine combined

Table 4 Standing heart rate. Effect of placebo, hydralazine, alinidine, propranolol, the combination of hydralazine and alinidine, and the combination of hydralazine and propranolol on heart rate (beats min^{-1}) in the standing position. Results are the mean ($\pm$ s.e. mean) of observations in five subjects

Treatment	Time after dosing (h)					
	0	1	2	3	4	6
Placebo	79.4 $\pm$ 3.9	76.8 $\pm$ 1.7	78.6 $\pm$ 3.0	75.2 $\pm$ 3.3	81.0 $\pm$ 5.7	84.2 $\pm$ 2.4
Hydralazine 50 mg	71.4 $\pm$ 6.5	83.4 $\pm$ 6.3 [†]	90.0 $\pm$ 7.0 ^{††}	89.8 $\pm$ 6.9 ^{††}	86.8 $\pm$ 9.1 ^{††}	84.0 $\pm$ 7.6 ^{††}
Alinidine 80 mg	79.2 $\pm$ 4.2	76.6 $\pm$ 4.3	77.2 $\pm$ 3.1	77.4 $\pm$ 1.8	74.8 $\pm$ 2.1	71.4 $\pm$ 3.2 ^{**}
Propranolol 40 mg	76.4 $\pm$ 6.5	64.8 $\pm$ 4.0 ^{††}	66.0 $\pm$ 3.6 ^{††}	65.0 $\pm$ 4.8 ^{††}	67.4 $\pm$ 4.2 ^{**}	72.6 $\pm$ 2.8 [*]
Hydralazine 50 mg Alinidine 80 mg	76.6 $\pm$ 6.7	83.2 $\pm$ 5.9	83.0 $\pm$ 3.9	86.6 $\pm$ 3.7 ^{††}	83.0 $\pm$ 4.0	80.2 $\pm$ 5.0
Hydralazine 50 mg Propranolol 40 mg	81.0 $\pm$ 4.0	71.2 $\pm$ 4.9 [†]	70.0 $\pm$ 4.9 [†]	70.6 $\pm$ 5.1 [†]	76.0 $\pm$ 5.4	77.8 $\pm$ 4.7

* $P < 0.05$, ** $P < 0.01$ when compared to placebo; [†] $P < 0.05$, ^{††} $P < 0.01$ when compared to the pre-treatment value.

Table 5 Exercise arterial pressure. Effect of placebo, hydralazine, alinidine, propranolol, the combination of hydralazine and alinidine, and the combination of hydralazine and propranolol on systolic and diastolic arterial pressure (mm Hg) during exercise. Results are the mean ($\pm$ s.e. mean) of observations in five subjects

Treatment	Time after dosing (h)						
	0	1	2	3	4	6	
Placebo	Systolic	154.0 ± 9.2	152.8 ± 9.2	163.2 ± 10.1	165.6 ± 10.2	162.4 ± 7.6	161.6 ± 4.2
	Diastolic	65.2 ± 11.2	77.6 ± 5.0	72.0 ± 7.6	67.6 ± 6.6	64.0 ± 5.5	56.8 ± 6.0
Hydralazine 50 mg	Systolic	155.2 ± 10.8	158.4 ± 11.0	149.8 ± 9.9	157.6 ± 7.4	152.8 ± 11.0	154.2 ± 9.6
	Diastolic	59.2 ± 7.9	57.2 ± 4.3	58.8 ± 5.1	68.4 ± 7.0	64.0 ± 7.7	60.4 ± 6.4
Alinidine 80 mg	Systolic	158.0 ± 12.0	164.5 ± 15.8	148.8 ± 17.2	146.4 ± 9.5	144.8 ± 10.6	148.2 ± 12.6
	Diastolic	48.8 ± 8.7	48.5 ± 7.9*	54.4 ± 11.3	46.0 ± 10.3	50.4 ± 12.7	45.6 ± 10.7
Propranolol 40 mg	Systolic	165.2 ± 12.4	135.2 ± 12.6†	133.8 ± 10.6††	141.6 ± 14.1	134.0 ± 5.8*†	133.2 ± 7.5*†
	Diastolic	70.4 ± 3.1	56.0 ± 11.3	53.2 ± 5.3	57.0 ± 6.0	63.8 ± 6.8	62.4 ± 5.5
Hydralazine 50 mg	Systolic	155.2 ± 12.7	154.4 ± 11.4	139.2 ± 8.9	139.6 ± 10.2	153.6 ± 7.4	153.8 ± 12.0
	Diastolic	61.4 ± 12.7	44.4 ± 2.0**	36.4 ± 8.4*††	52.0 ± 3.5	51.2 ± 7.9	54.0 ± 3.8
Hydralazine 50 mg	Systolic	176.4 ± 5.4	124.4 ± 16.2*††	119.2 ± 17.4*†††	124.4 ± 12.5*†††	133.6 ± 15.0*††	137.4 ± 15.2*††
	Diastolic	82.4 ± 5.7	45.6 ± 12.1*†††	62.4 ± 11.7	58.4 ± 10.2†	68.4 ± 11.8	65.4 ± 12.4

* $P < 0.05$, ** $P < 0.01$ when compared to placebo; † $P < 0.05$, †† $P < 0.01$ when compared to the pre-treatment value.

produced small reductions in systolic pressure, which were not significant, and reductions in diastolic pressure at 1 h ($P < 0.01$ when compared to placebo) and 2 h ($P < 0.01$ when compared to placebo, and $P < 0.05$ when compared to the pre-treatment value). Hydralazine and propranolol combined reduced systolic pressure at all time intervals after drug administration. These differences were significant at 1 and 4 h ($P < 0.05$ when compared to placebo, $P < 0.01$ when compared to the pre-treatment value), 2 and 3 h ($P < 0.01$ when compared to placebo, and to the pre-treatment value) and at 6 h ($P < 0.01$ when compared to the pre-treatment value); diastolic pressure was also reduced at 1 h ($P < 0.01$ when compared to placebo and to the pre-treatment value) and at 3 h ($P < 0.05$ when compared to the pre-treatment value). The reductions in systolic pressure produced by hydralazine and propranolol combined were greater than those produced by propranolol alone, but these differences were not significant.

Following placebo, there was no change in exercise heart rate (Table 6). Hydralazine alone did not change exercise heart rate. Alinidine reduced heart rate at 1 h ($P < 0.05$ when compared to placebo; $P < 0.01$ when compared to the pre-treatment value), and at 2, 3, 4 and 6 h ($P < 0.01$ when compared to placebo and to the pre-treatment value). Propranolol also reduced heart rate at all time intervals after drug administration ($P < 0.01$ when compared to placebo and to the pre-treatment value). The heart rate after propranolol was significantly less ($P < 0.05$) than that observed after alinidine at 1 and 2 h. The maximum reduction of exercise tachycardia after alinidine was observed at 3 h (17.4%) and the maximum reduction after propranolol at 2 h (17.3%).

Hydralazine and alinidine combined reduced heart rate at 1 h ($P < 0.01$ when compared to the pre-treatment value), at 2, 3 and 6 h ($P < 0.01$ when compared to placebo and to the pre-treatment value), and at 4 h ($P < 0.05$ when compared to placebo; $P < 0.01$ when compared to the pre-treatment value). The heart rate after hydralazine and alinidine combined was significantly greater ($P < 0.05$) than that observed after alinidine alone at 4 and 6 h. Hydralazine and propranolol combined reduced heart rate at all time intervals after drug administration ($P < 0.01$ when compared to placebo and to the pre-treatment value). There was no significant difference between the heart rates observed after hydralazine and propranolol combined, and those observed after propranolol alone.

Side effects

No side effects occurred in the placebo group. Two subjects reported tiredness on exercise following propranolol 40 mg. Two subjects reported facial flushing following hydralazine 50 mg; one of these

subjects also experienced headache and nasal stuffiness. Alinidine 80 mg produced tiredness in four subjects, and dry mouth in three of these four. Hydralazine 50 mg combined with propranolol 40 mg produced tiredness on exercise in three subjects, and one of these subjects also reported dyspepsia and headache. The combination of hydralazine 50 mg and alinidine 80 mg was poorly tolerated, producing side effects in all five subjects. The side effects were: dry mouth (four), tiredness (three), dizziness on standing (two), nausea (two), headache (one) and facial flushing (one). The dizziness on standing was accompanied by a marked fall in standing arterial pressure.

A further subject, not included in the analysis of results, developed severe postural hypotension 2 h after alinidine 80 mg, which persisted at 3 and 4 h, when he was too faint to exercise. At 6 h, he no longer felt faint, but still had dry mouth and marked postural fall in arterial pressure. As the subject had not in the course of the study received the combination of hydralazine and alinidine, he was withdrawn from the study.

Discussion

The increase in heart rate produced by exercise in man is due to a progressive increase in sympathetic activity as the level of exercise increases, accompanied by a gradual withdrawal of vagal parasympathetic tone (Robinson *et al.*, 1966; Pickering *et al.*, 1972). The tachycardia observed after vasodilator therapy is mainly due to increased sympathetic activity (Glick & Braunwald, 1965; O'Malley *et al.*, 1976; Davies *et al.*, 1979), although a reduction in vagal tone may contribute to the response (Mroczek *et al.*, 1976; Man in 'T Veld *et al.*, 1980). The tachycardia observed after hydralazine therapy is reduced by β -adrenoceptor blockade with propranolol (Brunner *et al.*, 1967; Zacest *et al.*, 1972; Velasco *et al.*, 1978), oxprenolol (Davies *et al.*, 1979) and alprenolol (Sannerstedt *et al.*, 1971). Hydralazine may also stimulate the heart directly (Gershwin & Smith, 1967; Khatri *et al.*, 1979; Wendling *et al.*, 1979) but studies on animal isolated preparations (Koch-Weser, 1974) and in normal man (Barbat *et al.*, 1981) indicate that such a direct effect occurs only at high doses. The tachycardia observed after hydralazine therapy may therefore be multifactorial, but the dominant mechanism is the increase in sympathetic tone.

In the present study, hydralazine produced small increases in supine heart rate, which were not significant when compared to placebo. In the standing position, heart rate was significantly increased when compared to placebo at 2 h ($P < 0.05$) and 3 h ($P < 0.01$) after hydralazine administration whereas arterial pressure at this time was unchanged. This would indicate that hydralazine does not inhibit the baro-

Table 6 Exercise heart rate. Effect of placebo, hydralazine, alinidine, propranolol, the combination of hydralazine and alinidine, and the combination of hydralazine and propranolol on heart rate (beats min^{-1}) after exercise. Results are the mean ($\pm$ s.e. mean) of observations in five subjects

Treatment	Time after dosing (h)					
	0	1	2	3	4	6
Placebo	146.0 $\pm$ 5.9	142.2 $\pm$ 4.0	145.8 $\pm$ 4.7	144.4 $\pm$ 6.6	144.0 $\pm$ 6.4	147.0 $\pm$ 5.1
Hydralazine 50 mg	143.2 $\pm$ 9.1	147.6 $\pm$ 8.0	145.6 $\pm$ 8.9	148.0 $\pm$ 8.0	147.8 $\pm$ 8.9	145.4 $\pm$ 10.0
Alinidine 80 mg	150.0 $\pm$ 3.4	131.6 $\pm$ 4.5 ^{††}	128.2 $\pm$ 3.0 ^{††}	123.8 $\pm$ 3.3 ^{††}	124.0 $\pm$ 4.1 ^{††}	127.0 $\pm$ 1.5 ^{††}
Propranolol 40 mg	145.0 $\pm$ 8.8	121.4 $\pm$ 6.9 ^{††}	119.4 $\pm$ 5.8 ^{††}	122.0 $\pm$ 5.1 ^{††}	125.0 $\pm$ 7.6 ^{††}	130.0 $\pm$ 8.7 ^{††}
Hydralazine 50 mg Alinidine 80 mg	149.0 $\pm$ 6.9	135.8 $\pm$ 5.8 ^{††}	134.6 $\pm$ 4.9 ^{††}	129.6 $\pm$ 3.2 ^{††}	136.0 $\pm$ 4.7 ^{††}	135.8 $\pm$ 3.7 ^{††}
Hydralazine 50 mg Propranolol 40 mg	149.6 $\pm$ 5.1	115.6 $\pm$ 7.8 ^{††}	118.2 $\pm$ 5.9 ^{††}	119.4 $\pm$ 2.8 ^{††}	124.4 $\pm$ 4.5 ^{††}	129.0 $\pm$ 5.7 ^{††}

* $P < 0.05$, ** $P < 0.01$ when compared to placebo; †† $P < 0.01$ when compared to the pre-treatment value.

receptor reflex mechanism. Hydralazine did not change arterial pressure or heart rate during exercise.

Propranolol and alinidine produced different effects on arterial pressure. Propranolol alone, and the combination of hydralazine and propranolol, produced small reductions in standing arterial pressure which were not significant when compared to placebo, and significantly reduced systolic arterial pressure after exercise. In contrast, alinidine alone, and the combination of hydralazine and alinidine, significantly reduced systolic and diastolic arterial pressure in the supine and standing position, and reduced diastolic arterial pressure after exercise. Our results confirm previous observations on the effect of alinidine 80 mg on arterial pressure in the supine and standing position (Harron *et al.*, 1982a). Alinidine 80 mg and propranolol 40 mg reduced heart rate in the supine position, and during exercise, to the same extent, but the maximum effect of alinidine on the exercise tachycardia was observed later than that of propranolol. Similar results were observed in a previous study (Harron *et al.*, 1981). In the standing position, propranolol significantly reduced heart rate at all time intervals after drug administration, whereas the effect of alinidine was less marked. Alinidine reduced systolic pressure in the standing position at 3, 4 and 6 h ($P < 0.05$ when compared to placebo) whereas heart rate was not significantly reduced ($P < 0.01$ when compared to placebo) until 6 h after drug administration. The fall in arterial pressure in the standing position produced by alinidine may elicit a reflex tachycardia, which may counteract any effect of alinidine to reduce heart rate, and account for the absence of effect of alinidine on heart rate prior to 6 h after drug administration.

The increase in heart rate in the standing position produced by hydralazine was abolished by propranolol, but not by alinidine. Hydralazine and alinidine

combined produced a fall in systolic arterial pressure in the standing position, whereas hydralazine alone produced no effect; this difference was significant ($P < 0.05$) at 2, 3, 4 and 6 h after drug administration. However, the increase in heart rate after combined therapy was less than that observed after hydralazine alone, although the difference was not significant. This would suggest that alinidine may also reduce a hydralazine tachycardia in man. In the conscious dog, the tachycardia following i.v. hydralazine is reduced by alinidine, although arterial pressure is also reduced (Kobinger *et al.*, 1979b).

Small amounts of clonidine are formed from alinidine in man, (Harron *et al.*, 1982b). It is unlikely that this clonidine contributes to the observed effects of alinidine as the peak plasma concentrations of clonidine occur later than the peak effect of alinidine, but the side effects from alinidine in the present study (dry mouth and tiredness) may have been due to the presence of clonidine. The high incidence of adverse effects in the subjects receiving hydralazine and alinidine combined may result from the marked fall in arterial pressure produced and the occurrence of side effects from both drugs.

Our study confirms previous observations that alinidine reduces resting and exercise heart rate in normal man, and reduces arterial pressure. Alinidine may also reduce a hydralazine tachycardia. Alinidine may therefore be of value in the treatment of arterial hypertension when given alone, or in combination with vasodilator therapy. Clinical studies will be required to see whether a dose of alinidine could be given to prevent reflex tachycardia, without causing marked side effects.

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