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Differential blockade of α-adrenoceptors by indoramin

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1 The effect of equihypotensive single oral doses of indoramin (mean dose 67 mg), phenoxybenzamine (mean dose 50 mg), hydralazine (mean dose 133 mg) and placebo on arterial pressure and heart rate in the supine and standing position was studied in six normal volunteers. Observations were made before and at 2 and 4 h after drug administration.

2 Plasma noradrenaline (NA) was measured at each time interval in the supine position, and after 4 min of standing. Plasma renin activity (PRA) was measured at each time interval after 30 min in the standing position.

3 The three active drugs reduced systolic arterial pressure in the standing position to a similar extent (indoramin, –24 mm Hg; phenoxybenzamine, –23.4 mm Hg; hydralazine, –30.4 mm Hg). The maximum effect of indoramin and phenoxybenzamine was observed at 4 h, and of hydralazine at 2 h after drug administration.

4 The reductions of arterial pressure in the standing position were accompanied by increases in heart rate, plasma NA and PRA. Small increases were observed after indoramin (heart rate, + 9.2 beats min^{-1}; plasma NA, + 126 pg/ml; PRA, + 0.33 ng angiotensin 1 ml^{-1} h^{-1}), greater increases after phenoxybenzamine (heart rate, + 20; plasma NA, + 210; PRA, + 0.47), and the greatest increases after hydralazine (heart rate, + 26; plasma NA, + 250; PRA, + 1.16).

5 In the supine position, indoramin and phenoxybenzamine produced no effect on arterial pressure, heart rate or plasma NA. Hydralazine produced small reductions in diastolic pressure, which were accompanied by an increase in heart rate of 25.5 beats min^{-1} ($P < 0.01$ when compared to placebo) and in plasma NA of 223 pg ml^{-1} ($P < 0.05$).

6 Plasma NA, PRA and heart rate increased together and may be regarded as three interdependent indices of sympathetic activity.

7 Indoramin reduced the degree of increase of plasma NA, PRA and heart rate per unit fall in pressure, when compared to phenoxybenzamine and hydralazine. The effect of phenoxybenzamine and hydralazine on the degree of increase was similar.

8 The results are consistent with the hypothesis that indoramin produces selective postsynaptic α_1-adrenoceptor blockade in man, and therefore produces relatively less tachycardia and NA increase than does a non-selective α-adrenoceptor antagonist (phenoxybenzamine) or an arteriolar vasodilator (hydralazine).

Keywords indoramin phenoxybenzamine hydralazine α-adrenoceptors

Introduction

Reduction of arterial pressure in man by hydralazine (Freis & Finnerty; 1950; Murphy *et al.*, 1982) or by phenoxybenzamine (Miller *et al.*, 1953; Skillman *et al.*, 1968) is accompanied by a reflex tachycardia. Indoramin is a selective postsynaptic α_1-adrenoceptor antagonist (Algate & Waterfall, 1978; Rhodes & Waterfall, 1978) which reduces arterial pressure with only a small increase in heart rate (Coltart, 1981; Nicholls *et al.*, 1981, 1983). The reason for the difference between indoramin and phenoxybenzamine may be related to differences in their effects on postsynaptic and presynaptic α-adrenoceptors. We wished to know if equihypotensive doses of indoramin, phenoxybenzamine and hydralazine would produce different effects on the sympathetic nervous system, as measured by changes in the heart rate, plasma noradrenaline, and plasma renin activity responses to upright posture.

Methods

Observations were made on six healthy male volunteers aged 18–27 years, mean weight 71.3 ± 2.5 kg (±s.e. mean) who gave written consent to the procedure which had been explained to them. The protocol of the study had been approved by the Ethical Committee of The Queen's University of Belfast. Subjects were asked to maintain a constant salt intake during the study period, to take their normal breakfast on each study day but to avoid caffeinated drinks, and to collect all urine voided in the 24 h preceding each study day, for estimation of Na^+ content. Three subjects were slow and three subjects were fast acetylators.

On each study day, a cannula was inserted into a forearm vein, and kept patent by the injection of small quantities of heparinised saline. After 15 min quiet supine rest, 10 ml of blood was withdrawn for estimation of plasma noradrenaline (NA). Heart rate (from lead I of a direct writing electrocardiograph) and arterial pressure (Hawksley random-zero sphygmomanometer) were recorded in duplicate. The subjects then sat upright for 1 min and stood for 3 min, when heart rate and arterial pressure were again recorded. Blood for plasma NA was withdrawn after 4 min of standing, and for plasma renin activity (PRA) after 30 min of standing. The subjects were then given a single oral dose of indoramin 50 mg, phenoxybenzamine 40 mg, hydralazine 100 mg or placebo at 09.00 h, administered in random order, double-blind, at weekly intervals. Observations were repeated at 2 h and 4 h after drug administration.

An independent observer analysed the results from the first part of the study. If the above doses of active drug had not produced a fall in systolic arterial pressure in the standing position of 20 mm Hg or more when compared to the pretreatment value, the observer prepared higher doses for administration on another study day. The higher doses were administered double-blind. In order to produce the required reduction of arterial pressure, three subjects were given indoramin 50 mg, two 75 mg, and one 100 mg (mean dose 67 mg); four subjects were given phenoxybenzamine 40 mg, one 60 mg, and one 80 mg (mean dose 50 mg); and three subjects were given hydralazine 100 mg, two 150 mg, and one 200 mg (mean dose 133 mg).

Blood samples for NA measurement were anticoagulated with heparin, and the 10 ml sample tubes contained 5 mg of sodium metabisulphite as an anti-oxidant. Blood samples for PRA were anticoagulated with 15 mg/10 ml glass tube of EDTA tetrasodium salt. All samples were plunged immediately into ice, centrifuged at 4°C, the plasma removed for analysis, and stored at –40°C for not longer than 1 month.

Plasma NA was measured by a modification of the method of Krstulovic *et al.* (1981) as follows: To 2 ml volumes of plasma was added 2.0 ng of 3,4 dihydroxybenzylamine (Sigma Chemical Co.) as internal standard, followed by 15 mg of acid-washed alumina (Bioanalytical Systems, West Lafayette, IN 47906, U.S.A.) and 1.0 ml of Tris buffer, 1.5 M, pH 8.5 (Sigma Chemical Co.). The tubes were immediately vortexed for 5 s and mixed for a further 5 min on a rotary mixer. The alumina was allowed to settle and the supernatant aspirated to waste. The alumina was washed twice with double glass-distilled water. After centrifugation the washing was discarded and the catecholamines eluted with 100 μl of 0.1 M acetic acid. 50 μl of clear supernatant was injected on the h.p.l.c. column. The column used was 25 cm × 0.46 cm stainless steel, packed with Hypersil 5 μ ODS (Shandon Southern Products, Runcorn, Cheshire, England). The eluent consisted of potassium dihydrogen orthophosphate (0.035 M), citric acid (0.03 M), octane sulphonic acid (0.0022 M), modified with 12% methanol. Flow-rate was 1.5 ml/min and detection was made on a model LC-4B/17 electrochemical detector with a LC-15 glassy carbon electrode (Bioanalytical Systems, West Lafayette, IN 47906, U.S.A.). Applied voltage was + 0.5 V *vs* an Ag/AgCl reference electrode, detector sensitivity was set at 1 nA/V. Detected peaks were recorded on a Perkin-Elmer model 056 chart recorder. Coefficient of variation for

the assay was 7% and inter-assay variation was 8%. Sensitivity for adrenaline was 40 pg ml^{-1}, and for noradrenaline 30 pg ml^{-1}.

PRA was expressed as ng angiotensin I generated ml^{-1} plasma h^{-1} at pH 7.4 and 37°C. Angiotensin I was measured by radioimmunoassay using a GammaCoat Kit (Clinical Assays, Travenol Laboratories Inc.), after the method of Haber *et al.* (1969).

Results are expressed as the mean ± s.e. mean. Statistical analyses were carried out using analysis of variance, and Duncan's multiple range test used to compare mean values. A P value of less than 0.05 was regarded as significant. 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

There was no change in arterial pressure or heart rate in the supine position throughout the study period after placebo administration (Table 1). Plasma NA levels increased during the course of the study, but this increase was not significant. Indoramin (mean dose 67 mg) produced no effect on arterial pressure or heart rate, and the increase in NA levels was similar to that observed after placebo administration. Phenoxybenzamine (mean dose 50 mg) had no effect on systolic arterial pressure or heart rate. Diastolic arterial pressure prior to the administration of phenoxybenzamine and at 4 h after drug administration was significantly lower than the corresponding placebo value. Plasma NA levels were lower than those observed after placebo administration, but these differences were not significant; the levels rose during the course of the study. Hydralazine (mean dose 133 mg) had no effect on systolic arterial pressure, and reduced diastolic pressure at 2 h ($P < 0.05$ when compared to the pre-treatment value) and 4 h ($P < 0.05$) when compared to placebo) after drug administration. These reductions were associated with increases in heart rate ($P < 0.01$) and plasma NA levels ($P < 0.05$) at 2 and 4 h after administration of hydralazine.

Standing position

Arterial pressure and heart rate in the standing position did not change after placebo administration (Table 2). Plasma NA levels were significantly greater at all time intervals than those observed in the supine position ($P < 0.01$). Indoramin significantly reduced systolic and diastolic arterial pressure at 4 h after drug administration. These reductions were associated with small increases in heart rate and plasma NA levels, which were not significantly different from the corresponding placebo values. Phenoxybenzamine significantly reduced systolic and diastolic arterial pressure, and heart rate was significantly increased at 4 h after drug administration. Plasma NA levels were increased, but these differences were not significant. Hydralazine significantly reduced systolic and diastolic arterial pressure at 2 and 4 h after drug administration, with the maximum effect observed at 2 h. Significant increases in heart rate were observed at both times. Plasma NA levels were significantly increased at 2 and 4 h after admin-

Table 1 Effect of placebo, indoramin (mean dose 67 mg), phenoxybenzamine (mean dose 50 mg) and hydralazine (mean dose 133 mg) on systolic and diastolic arterial pressure, heart rate and plasma noradrenaline (NA) in the supine position

Drug	*Time (h)*	*Systolic (mm Hg)*	*Diastolic (mm Hg)*	*Heart rate (beats min^{-1})*	*Plasma NA (pg/ml)*
Placebo	0	117.7 ± 6.1	66.7 ± 5.3	62.8 ± 4.9	210.2 ± 55.6
	2	114.7 ± 3.7	65.7 ± 3.1	60.2 ± 3.7	249.0 ± 59.8
	4	115.7 ± 3.8	71.0 ± 2.8	61.8 ± 5.3	268.3 ± 67.8
Indoramin	0	116.7 ± 3.7	68.0 ± 2.4	59.8 ± 2.9	174.2 ± 32.1
	2	117.3 ± 4.0	72.0 ± 3.2	57.7 ± 1.8	226.0 ± 53.0
	4	117.0 ± 4.8	69.0 ± 3.2	58.3 ± 2.6	260.5 ± 68.4
Phenoxybenzamine	0	112.0 ± 4.1	59.3 ± 2.9*	58.0 ± 3.4	139.5 ± 21.8
	2	112.0 ± 3.4	66.0 ± 3.1†	59.2 ± 2.5	179.3 ± 30.8
	4	113.0 ± 4.3	62.0 ± 2.3*	58.3 ± 1.5	217.8 ± 53.2
Hydralazine	0	118.7 ± 4.3	70.0 ± 2.9	56.8 ± 3.0	211.2 ± 34.3
	2	120.0 ± 6.5	60.7 ± 2.7†	82.3 ± 5.1**††	433.8 ± 84.0*
	4	119.3 ± 6.2	63.7 ± 5.7*	79.5 ± 5.7**††	496.5 ± 117.8*

Means ± s.e. mean are indicated ($n = 6$). *$P < 0.05$, **$P < 0.01$ when compared to placebo. †$P < 0.05$, ††$P < 0.01$ when compared to the pre-treatment value.

Table 2 Effect of placebo, indoramin (mean dose 67 mg), phenoxybenzamine (mean dose 50 mg) and hydralazine (mean dose 133 mg) on systolic and diastolic arterial pressure, heart rate and plasma noradrenaline (NA) in the standing position

Drug	*Time (h)*	*Systolic (mm Hg)*	*Diastolic (mm Hg)*	*Heart rate (beats min^{-1})*	*Plasma NA (pg/ml)*
Placebo	0	118.7 ± 3.6	77.0 ± 5.2	86.7 ± 5.1	365.2 ± 57.3
	2	113.7 ± 3.0	80.7 ± 3.5	83.8 ± 5.7	395.0 ± 66.4
	4	117.0 ± 4.2	80.3 ± 3.5	81.3 ± 6.7	340.5 ± 46.5
Indoramin	0	116.0 ± 2.5	80.3 ± 3.3	79.0 ± 6.0	347.8 ± 25.3
	2	103.3 ± 5.2	71.3 ± 5.6	85.7 ± 8.8	441.3 ± 66.3
	4	92.0 ± 7.5**†	55.3 ± 5.3**††	88.2 ± 8.2	473.7 ± 88.2
Phenoxy-benzamine	0	120.7 ± 3.7	79.7 ± 3.4	81.0 ± 7.1	292.7 ± 37.1
	2	104.0 ± 5.1†	74.3 ± 3.6	86.7 ± 4.2	405.3 ± 56.8
	4	97.3 ± 3.7*†	65.0 ± 4.9*	101.0 ± 5.5*†	502.8 ± 55.8
Hydralazine	0	121.7 ± 3.9	84.3 ± 3.6	80.3 ± 4.7	370.8 ± 49.7
	2	91.3 ± 6.5*††	53.3 ± 6.5**††	106.3 ± 5.3*††	620.8 ± 69.9*†
	4	104.3 ± 4.0†	64.7 ± 3.3*†	100.5 ± 6.5*†	778.4 ± 184.8**††

Means ± s.e. mean are indicated ($n = 6$). *$P < 0.05$, **$P < 0.01$ when compared to placebo. †$P < 0.05$, ††$P < 0.01$ when compared to the pre-treatment value.

istration of hydralazine. The maximum reduction of systolic arterial pressure produced by hydralazine (–30.4 mm Hg at 2 h) was not significantly different from that produced by phenoxybenzamine (–23.4 mm Hg at 4 h) or indoramin (–24.0 mm Hg at 4 h after drug administration).

PRA was greater at 2 h, and unchanged at 4 h after placebo administration (Table 3). Indoramin produced small increases in PRA, which were not significant. Phenoxybenzamine significantly increased PRA at 4 h, and hydralazine significantly increased PRA at 2 and 4 h after drug administration. The 24 h urinary Na^+ excretion was greater in the hydralazine treatment group, but this difference was not significant.

Figure 1 shows the mean plasma NA concentrations and the mean systolic arterial pressures in the standing position before drug administration, and at the time of maximum reduction of pressure. Plasma NA increased by a mean of 5.25 pg/mm Hg fall in systolic pressure after indoramin. This was less than the increases after phenoxybenzamine (8.98) or hydralazine (8.22 pg/mm Hg fall). Figure 2 shows the mean PRA and mean systolic pressure before drug administration and at the time of maximum reduction of pressure. PRA increased by a mean of 0.014 ng angiotensin I ml^{-1} plasma h^{-1} per mm Hg fall after indoramin. This was less than the increases observed after phenoxybenzamine (0.02) and hydralazine (0.38). Figure 3 shows the mean heart rates and mean systolic pressures before drug administration and the time of maximum reduction of pressure. Heart rate increased by 0.38 beats min^{-1} per mm Hg fall in pressure after indoramin, which was less than the increases after phenoxybenzamine (0.85) and hydralazine (0.86).

Side-effects

No side effects were observed after placebo administration. After indoramin, four subjects felt faint on standing, but no syncopal episodes occurred. Two subjects had received 50 mg, one 75 mg and one 100 mg. Three subjects felt tired (one had received 50 mg, and two 75 mg). After phenoxybenzamine, four subjects reported nasal

Table 3 Effect of placebo, indoramin (mean dose 67 mg), phenoxybenzamine (mean dose 50 mg) and hydralazine (mean dose 133 mg) on plasma renin activity (PRA; ng angiotensin I generated ml^{-1} plasma h^{-1}). Also shown is the 24 h urinary sodium excretion (Na^+, mmol) at the time of sampling for PRA.

	0h	*2h*	*4h*	*Na^+*
Placebo	0.95 ± 0.36	1.40 ± 0.24	0.87 ± 0.14	113.2 ± 14.2
Indoramin	1.02 ± 0.25	1.41 ± 0.19	1.35 ± 0.15	138.8 ± 15.8
Phenoxybenzamine	1.14 ± 0.30	1.43 ± 0.36	1.61 ± 0.33*	134.8 ± 29.3
Hydralazine	1.09 ± 0.37	2.25 ± 0.80*††	2.10 ± 0.62**††	169.5 ± 43.6

Means ± s.e. mean are indicated ($n = 6$). *$P < 0.05$, **$P < 0.01$ when compared to placebo. ††$P < 0.01$ when compared to the pre-treatment value.

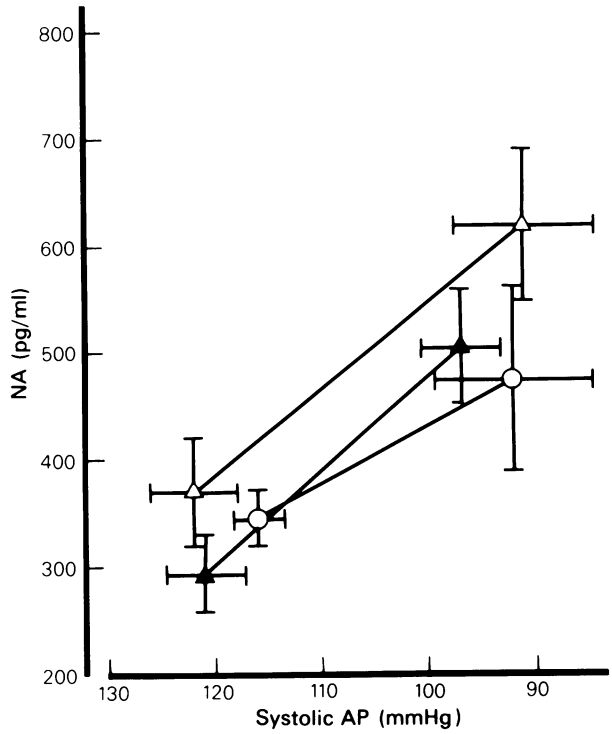

Figure 1 Effect of indoramin (○—○) (mean dose 67 mg), phenoxybenzamine (mean dose 50 mg) (▲—▲) and hydralazine (mean dose 133 mg) (△—△) on plasma noradrenaline (NA, pg/ml) and systolic arterial pressure (AP, mm Hg) in the standing position. Means ± s.e. mean are indicated (n = 6).

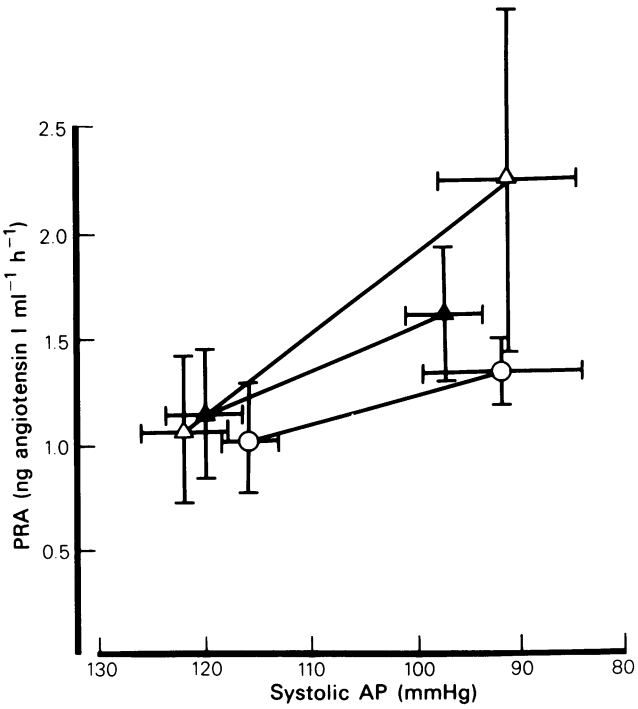

Figure 2 Effect of indoramin (○—○) (mean dose 67 mg), phenoxybenzamine (mean dose 50 mg) (▲—▲) and hydralazine (mean dose 133 mg) (△—△) on plasma renin activity (PRA, ng angiotensin I ml^{-1} plasma h^{-1}) and systolic arterial pressure (AP, mm Hg) in the standing position. Means ± s.e. mean are indicated (n = 6).

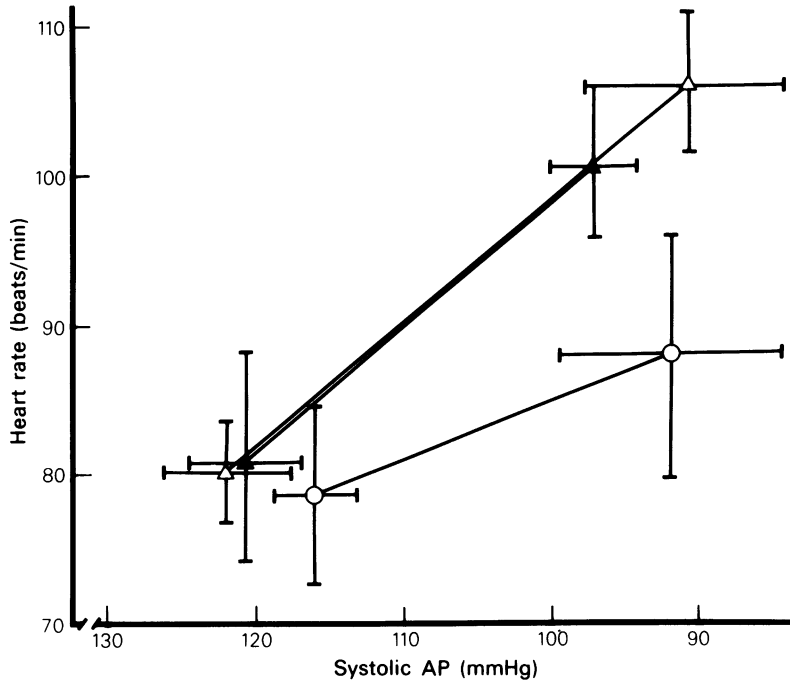

Figure 3 Effect of indoramin (○—○) (mean dose 67 mg), phenoxybenzamine (mean dose 50 mg) (▲—▲) and hydralazine (mean dose 133 mg) (△—△) on heart rate (HR, beats min^{-1}) and systolic arterial pressure (AP, mm Hg) in the standing position. Means ± s.e. mean are indicated ($n = 6$).

congestion; two had received 40 mg, one 60 mg, and one 80 mg. Two subjects felt faint on standing (both after 40 mg), and two felt tired (one after 40 mg and one after 80 mg). Hydralazine produced side effects in all subjects; these were facial flushing (five), headache (four), faintness on standing (three), nasal congestion (three), palpitations (two), shivering (two), tiredness (one) and dyspnoea (one).

Discussion

Plasma NA is derived from the peripheral sympathetic nervous system (von Euler *et al.*, 1954; Glowinski *et al.*, 1965; Cryer, 1976) and reflects the activity of the system (Lake *et al.*, 1976; Kopin *et al.*, 1978; Saar & Gordon, 1979; Watson *et al.*, 1979; Kiowski *et al.*, 1981), although some care may be necessary in interpretation of the results due to different patterns of organ release and extraction (Brown *et al.*, 1981). Secretion of renin is partly under the control of the sympathetic nervous system (Gordon *et al.*, 1967; Winer *et al.*, 1969) so that PRA is also a marker of sympathetic activity (Kotchen *et al.*, 1971), but other factors such as local renal haemodynamics (Pettinger *et al.*, 1973; Mathias *et al.*, 1975) and sodium intake (Watson *et al.*, 1980) may also influence PRA. The increase in heart rate observed after vasodilator therapy is mainly due to an increase in sympathetic activity (Davies *et al.*, 1979) but a reduction in vagal tone and other effects may also be present (Mroczec *et al.*, 1976; Man in 'T Veld *et al.*, 1980; Spokas & Wang, 1980). Plasma NA, PRA and heart rate are therefore interdependent variables, and individually may not be wholly accurate as a reflection of sympathetic activity. Plasma adrenaline levels are not associated with an increase in heart rate until the concentration exceeds 50 pg ml^{-1} (Clutter *et al.*, 1980). In our study, the levels rarely rose above the limit of sensitivity for the assay (40 pg ml^{-1}).

In the present study, no change in plasma NA or heart rate in the supine position was observed after administration of indoramin or phenoxybenzamine, whereas both were increased after hydralazine. In the standing position, increases in plasma NA, heart rate and PRA were observed after all three drugs. Indoramin and phenoxybenzamine are both α-adrenoceptor antagonists (Doxey *et al.*, 1977; Algate & Waterfall, 1978), and so the effects of these drugs are observed when the sympathetic system is activated, such as when assuming the erect

position. Hydralazine is a direct arteriolar vasodilator which does not interact with α-adrenoceptors (Koch-Weser, 1976; Worcel, 1978), and as the action of hydralazine is independent of a functioning sympathetic nervous system, it would be expected that changes would be observed in both the supine and standing positions.

In the standing position, the three active drugs produced similar reductions of arterial pressure (Table 2). A small increase in heart rate was observed after indoramin, and significant increases after phenoxybenzamine and hydralazine. Small increases of plasma NA and PRA (Table 3) were observed after indoramin and phenoxybenzamine, and significant increases after hydralazine. Although the increases of plasma NA and PRA produced by indoramin and phenoxybenzamine were similar, the rate of increase per mm Hg fall of arterial pressure was different (Figures 1, 2 and 3), suggesting that there may be a difference of effect on the sympathetic system of the two drugs.

Indoramin is a selective α_1-adrenoceptor antagonist (Algate & Waterfall, 1978; Rhodes & Waterfall, 1978; U'Prichard *et al.*, 1978). Although phenoxybenzamine is relatively selective for α_1-adrenoceptors (Dubocovich & Langer, 1972; Doxey *et al.*, 1977; Constantine & Lebel, 1980), at the doses used in the present study (0.5–1.1 mg kg^{-1}) it would be expected to produce α_2-adrenoceptor blockade in addition (Hamilton *et al.*, 1981). It has been suggested that drugs which are selective postsynaptic α_1-adrenoceptor antagonists (such as indoramin and prazosin) are less likely to increase heart rate in clinical use, as the negative feedback inhibition of NA release mediated by presynaptic α_2-adrenoceptors is left intact (Hoffman & Lefkowitz, 1980). Numerous studies have demonstrated *in vitro* the role of the α_2-adrenoceptors in the regulation of NA release (Lokhandwala & Buckley, 1976; Langer, 1977; Yamaguchi *et al.*, 1977; Lefèvre-Borg *et al.*, 1978), although the degree of regulation may be limited in extent (Drew, 1980; Reid & Hamilton, 1980; Angus & Korner, 1980; Kalsner *et al.*, 1980). The selectivity of an antagonist for α_1- or α_2-adrenoceptors may vary between different species (Roach *et al.*, 1978) and it is not always possible to demonstrate differential α-adrenoceptor blockade *in vivo* (Commarato *et al.*, 1977; Atkins & Nicolosi, 1979). In other animal studies, different effects of selective and non-selective α-adrenoceptor blockade on heart rate and plasma NA were demonstrated, indicating that selective drugs may produce lesser increases of heart rate and plasma NA for a given reduction of arterial pressure (Graham & Pettinger, 1979; Graham *et al.*, 1980; Saeed *et al.*, 1982).

It has proved difficult to demonstrate differential α-adrenoceptor blockade in man. In normal man, administration of the α_2-adrenoceptor agonist α-methyl-NA does not change plasma NA clearance, suggesting that α_2-adrenoceptors may not be involved in the regulation of plasma NA levels (Fitzgerald *et al.*, 1981). In hypertensive man, the effects of the selective α_1-adrenoceptor antagonist prazosin (Cambridge *et al.*, 1977) have been compared with those of phenoxybenzamine after single dose (Mulvihill-Wilson *et al.*, 1983) and repeated administration (Mulvihill-Wilson *et al.*, 1979). After acute administration, heart rate and plasma NA changes were greater after prazosin than after phenoxybenzamine, but tachycardia observed after the first dose of prazosin may be due in part to venodilation (Nicholls *et al.*, 1981). After chronic administration for 4 weeks, the heart rate after prazosin was similar to pre-treatment values, whereas heart rate was still increased after phenoxybenzamine, despite a smaller reduction of arterial pressure. Prazosin reduced systolic pressure in the standing position by 23.4 mm Hg; plasma NA levels increased by 17.2 pg per mm Hg fall in pressure and heart rate increased by 0.24 beats min^{-1} per mm Hg. In contrast, phenoxybenzamine reduced systolic pressure by 11.9 mm Hg, but plasma NA levels increased by 39.9 pg per mm Hg, and heart rate by 1.12 beats min^{-1} per mm Hg.

Both prazosin and indoramin are selective α_1-adrenoceptor antagonists, and the results of these studies in hypertensive man and of the present study are consistent with the hypothesis that selective α-adrenoceptor blockade may modify the heart rate and catecholamine responses to induced hypotension in man. However, indoramin has other actions which may also contribute to a reduction of heart rate, such as a direct action on the myocardium (Algate *et al.*, 1981), a potent antihistamine effect (Alps *et al.*, 1972) and possible central effects (Baum & Shropshire, 1975). The reason for the relative lack of tachycardia after indoramin administration therefore remains unclear, but it is possible that the mechanism of differential blockade of α-adrenoceptors may be in part responsible.

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