Effect of indoramin, labetalol and alinidine on sympathetic function in normal man

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1 The effects of single oral doses of indoramin (mean dose 58 mg), labetalol (mean dose 150 mg), alinidine 80 mg and placebo on arterial pressure and heart rate in the supine and standing positions were studied in six normal volunteers. Doses were chosen to give equivalent reductions of arterial pressure in the standing position. 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 In the supine position, alinidine produced a significant reduction of systolic arterial pressure from 124.0 ± 3.0 mm Hg to 104.3 ± 4.1 mm Hg at 2 h ($P < 0.01$) and to 101.7 ± 2.2 mm Hg at 4 h ($P < 0.01$). Diastolic pressure was reduced from 74.7 ± 2.6 mm Hg to 57.0 ± 4.6 mm Hg at 4 h ($P < 0.01$). Arterial pressure was unchanged after indoramin or labetalol administration.

4 In the supine position, heart rate was unchanged after indoramin, and small reductions were observed after labetalol and alinidine. Indoramin produced a significant increase in plasma NA. A small increase of plasma NA was observed after labetalol, and a small decrease after alinidine.

5 In the standing position, the three active drugs reduced systolic arterial pressure to a similar extent (indoramin, -26.7 mm Hg at 4 h after drug administration; labetalol, -21.3 mm Hg at 2 h; alinidine, -21.7 mm Hg at 4 h).

6 In the standing position, heart rate was increased by indoramin ($+6.6$ beats min^{-1} at the time of maximum arterial pressure reduction) but reduced by labetalol (-10.4 beats min^{-1}) and alinidine (-7.6 beats min^{-1}). Plasma NA was increased after indoramin and labetalol ($+191$ and $+137$ pg ml^{-1} respectively) but a small reduction was observed after alinidine (-128 pg ml^{-1}). PRA was unchanged after labetalol. A small increase of PRA was observed after indoramin, and a significant increase after alinidine administration (1.29 ± 0.16 to 2.32 ± 0.44 ng angiotensin I $\text{ml}^{-1} \text{h}^{-1}$ at 2 h, $P < 0.05$).

7 The effects of indoramin and labetalol may be correlated with their known pharmacological properties. Alinidine produced small reductions of heart rate and plasma NA, and an increase of PRA. The mechanism of the hypotensive action of alinidine is unknown, but these results suggest the possibility that reduction of sympathetic activity may be a component of this action.

Keywords indoramin labetalol alinidine sympathetic function

Introduction

The reduction of arterial pressure in man is usually accompanied by a reflex tachycardia (Marey, 1863), but indoramin, labetalol and alinidine reduce arterial pressure with only small changes in heart rate. The mechanism of action of these three drugs is different. Indoramin reduces arterial pressure by producing competitive blockade of vascular α -adrenoceptors, and this reduction is accompanied by small increases in heart rate (Nicholls *et al.*, 1983a). The reason for the relative lack of tachycardia after indoramin administration is not clear, but possible mechanisms are selective blockade of post-synaptic α_1 -adrenoceptors (Algate & Waterfall, 1978; Rhodes & Waterfall 1978; Nicholls *et al.*, 1984) or a direct bradycardic action (Alps *et al.*, 1972). Labetalol reduces arterial pressure in man through α -adrenoceptor blockade, and the reduction is not accompanied by an increase in heart rate, as the reflex tachycardia is prevented by concomitant β -adrenoceptor blockade (Boakes *et al.*, 1971; Richards *et al.*, 1974; 1977). Alinidine reduces arterial pressure in normal man by an unknown mechanism (Harron *et al.*, 1982a; Nicholls *et al.*, 1983b) and reduces heart rate by a direct action on the sino-atrial node (Kobinger *et al.*, 1979a, b).

As the three drugs prevent an increase in heart rate in response to a fall in arterial pressure by different mechanisms, we wished to compare the effects of the drugs on sympathetic activity. In this study, we have examined the effects of equi-hypotensive doses of indoramin, labetalol and alinidine on heart rate and plasma noradrenaline and renin activity in normal man.

Methods

Observations were made in six healthy male volunteers aged 18–24 years, mean weight 77.7 ± 2.9 kg ($\pm$ 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. All subjects had a physical examination, and a normal ECG and biochemical and haematological profile prior to entry to the study. Subjects were asked to take a constant salt intake during the study period, to take their normal breakfast 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.

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 blood was withdrawn for estimation of plasma noradrenaline (NA). Heart rate (from lead I of a direct-reading 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, following which 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, labetalol 100 mg, alinidine 80 mg or placebo, administered in random order, double-blind, at weekly intervals. Observations were repeated at 2 and 4 h after drug administration.

An independent observer analysed the effects of the different treatments on arterial pressure. If the 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 pre-treatment value, the observer prepared higher doses for administration on a subsequent study day. The higher doses were again administered double-blind. In order to produce the required reduction of arterial pressure, five subjects received indoramin 50 mg and one 100 mg (mean dose 58 mg), three subjects labetalol 100 mg and three 200 mg (mean dose 150 mg), and all six subjects received alinidine 80 mg.

Blood samples for measurement of NA concentration were collected into heparinised tubes containing 5 mg sodium metabisulphite as an anti-oxidant. Blood samples for PRA were anticoagulated with 15 mg of EDTA tetrasodium salt per 10 ml glass tube. All samples were plunged immediately into ice, centrifuged at 4°C, the plasma removed for analysis, and stored at -40°C for up to 1 month. Plasma NA concentrations were measured by a modified high performance liquid chromatographic method including an electrochemical detector (Krstulović *et al.*, 1981; Nicholls *et al.*, 1984). 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 per ml 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 $\pm$ s.e.

mean. Statistical analyses were carried out using analysis of variance, and Duncan's multiple range test was employed 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 observed after placebo administration, and with the pre-treatment values.

Results

Supine position

There were no changes in arterial pressure, heart rate or plasma NA concentration in the supine position after placebo administration (Table 1). Indoramin (mean dose 58 mg) produced no effect on arterial pressure or heart rate, but plasma NA concentration was increased at 4 h after drug administration (*P* < 0.05). Labetalol (mean dose 150 mg) produced small reductions in diastolic arterial pressure and heart rate, and a small increase in plasma NA concentration, which were not significant. Alinidine significantly reduced systolic and diastolic arterial pressure at 4 h and systolic pressure at 2 h after drug administration. These effects were accompanied by small reductions in heart rate and plasma NA concentrations, which were not significant.

Standing position

There were no changes in arterial pressure,

heart rate or plasma NA concentration in the standing position after placebo administration (Table 2). Plasma NA concentrations were significantly greater at the three observation times than those observed in the supine position. Indoramin reduced systolic and diastolic arterial pressure significantly, with small increases in heart rate and plasma NA concentration. Labetalol significantly reduced systolic and diastolic arterial pressure, with a reduction in heart rate and an increase in plasma NA concentration. Alinidine significantly reduced systolic and diastolic arterial pressure, with a small reduction in heart rate, and a small reduction in plasma NA concentration. The maximum reduction of systolic arterial pressure produced by indoramin (−26.7 mm Hg at 4 h) was not significantly different from that produced by labetalol (−21.3 mm Hg at 2 h) or alinidine (−21.7 mm Hg at 4 h), whereas the three active drugs produced different effects on heart rate (indoramin, +6.6 beats min^{−1}; labetalol, −10.4; alinidine, −7.6) and plasma NA concentration (indoramin, +191 pg ml^{−1}; labetalol, +136.8; alinidine, −128.1).

PRA was unchanged after placebo administration (Table 3). The 24 h urinary Na⁺ excretion was greater in the indoramin treatment group, but this difference was not significant. Indoramin increased PRA at 2 h but not at 4 h after drug administration. Labetalol produced no effect on PRA. Alinidine increased PRA at 2 h after drug administration (*P* < 0.05), and also produced a small increase at 4 h.

Table 1 Effect of placebo, indoramin (mean dose 58 mg), labetalol 150 mg and alinidine 80 mg on systolic and diastolic arterial pressure, heart rate and plasma noradrenaline (NA) in the supine position. Means ± s.e. mean are indicated (*n* = 6).

Drug	Time (h)	Blood pressure		Heart rate (beats min ^{−1})	Plasma NA (pg/ml)
		Systolic (mm Hg)	Diastolic (mm Hg)		
Placebo	0	125.3 ± 3.4	69.7 ± 2.6	74.5 ± 3.6	217.5 ± 21.1
	2	120.0 ± 2.5	71.3 ± 2.5	71.7 ± 4.7	190.0 ± 24.5
	4	119.0 ± 2.8	74.0 ± 3.1	72.8 ± 4.6	215.3 ± 27.7
Indoramin	0	120.3 ± 2.2	69.0 ± 4.3	69.2 ± 4.1	180.7 ± 25.2
	2	115.7 ± 4.6	69.0 ± 1.9	72.8 ± 3.8	267.0 ± 35.0†
	4	118.7 ± 4.5	67.7 ± 4.3	70.8 ± 4.0	303.7 ± 43.8*†
Labetalol	0	116.3 ± 4.0*	68.7 ± 1.1	80.8 ± 3.4	220.5 ± 17.6
	2	113.0 ± 2.7	63.3 ± 1.2	74.5 ± 5.4	264.2 ± 41.2
	4	112.3 ± 2.9	65.0 ± 1.9*	70.0 ± 4.4†	282.5 ± 39.7
Alinidine	0	124.0 ± 3.0	74.7 ± 2.6	73.8 ± 4.4	231.7 ± 33.9
	2	104.3 ± 4.1**††	64.7 ± 4.0	66.2 ± 3.3	158.5 ± 10.2
	4	101.7 ± 2.2**††	57.0 ± 4.6**††	65.0 ± 1.1	195.0 ± 43.3

P* < 0.05, *P* < 0.01 when compared to placebo. † = *P* < 0.05, †† = *P* < 0.01 when compared to pretreatment value

Table 2 Effect of placebo, indoramin (mean dose 58 mg), labetalol 150 mg and alinidine 80 mg on systolic and diastolic arterial pressure, heart rate and plasma noradrenaline (NA) in the standing position. Means $\pm$ s.e. mean are indicated ($n = 6$).

Drug	Time (h)	Blood pressure		Heart rate (beats min ⁻¹)	Plasma NA (pg/ml)
		Systolic (mm Hg)	Diastolic (mm Hg)		
Placebo	0	119.3 $\pm$ 3.2	79.3 $\pm$ 3.2	97.5 $\pm$ 2.3	368.6 $\pm$ 50.0
	2	121.0 $\pm$ 3.4	81.3 $\pm$ 1.7	96.3 $\pm$ 3.6	396.0 $\pm$ 40.3
	4	117.3 $\pm$ 3.5	82.0 $\pm$ 2.1	100.2 $\pm$ 4.3	425.0 $\pm$ 50.0
Indoramin	0	129.7 $\pm$ 4.2	83.3 $\pm$ 4.5	91.7 $\pm$ 4.0	327.2 $\pm$ 41.1
	2	103.7 $\pm$ 8.4* $\dagger\dagger$	65.7 $\pm$ 7.2* $\dagger$	93.0 $\pm$ 9.0	398.8 $\pm$ 26.6
	4	103.0 $\pm$ 2.3* $\dagger\dagger$	69.0 $\pm$ 3.6* $\dagger$	98.3 $\pm$ 7.2	518.2 $\pm$ 73.1 $\dagger$
Labetalol	0	122.3 $\pm$ 5.7	78.3 $\pm$ 3.3	101.7 $\pm$ 4.6	421.2 $\pm$ 49.5
	2	101.0 $\pm$ 4.1* $\dagger$	67.3 $\pm$ 2.1*	91.3 $\pm$ 5.7	558.0 $\pm$ 91.9*
	4	108.0 $\pm$ 6.5 $\dagger$	69.0 $\pm$ 4.0*	88.0 $\pm$ 5.4 $\dagger$	547.5 $\pm$ 86.7
Alinidine	0	119.3 $\pm$ 2.5	78.3 $\pm$ 3.1	96.3 $\pm$ 7.7	500.3 $\pm$ 65.2
	2	98.7 $\pm$ 4.6* $\dagger$	68.0 $\pm$ 2.8*	88.0 $\pm$ 5.4	307.0 $\pm$ 38.1 $\dagger$
	4	97.6 $\pm$ 3.3* $\dagger$	67.7 $\pm$ 2.7*	88.7 $\pm$ 5.8	372.2 $\pm$ 86.7

* $P < 0.05$, ** $P < 0.01$ when compared to placebo. $\dagger = P < 0.05$, $\dagger\dagger = P < 0.01$ when compared to the pretreatment value

Side effects

There were no side effects reported after placebo administration. Indoramin produced side effects in five subjects, consisting of dizziness without syncope (3), tiredness (2), nasal congestion (1) and palpitations (1). Labetalol produced side effects in two subjects; one felt dizzy, and the other felt tired, and noted scalp tingling. Alinidine produced tiredness in all subjects, and one also noted a dry mouth. Tiredness after alinidine administration was noted by four subjects at 2 h and by two subjects at 4 h.

Discussion

This study confirms previous observations that indoramin reduces arterial pressure in normal man in the standing position, and that this

reduction is accompanied by only a small increase in heart rate (Coltart, 1981; Nicholls *et al.*, 1983a). Labetalol also reduced arterial pressure in the standing position, and this was accompanied by a small reduction of heart rate. These results are similar to those reported in a previous study, in which labetalol reduced arterial pressure in normal man in the sitting position, with no change in heart rate (Richards *et al.*, 1974). The present study also confirms that alinidine reduces systolic and diastolic arterial pressure in the supine and standing positions, and that these reductions are accompanied by small reductions in heart rate (Harron *et al.*, 1982a; Nicholls *et al.*, 1983b).

Plasma NA is derived from the sympathetic nervous system, and the concentration is therefore determined by the rate of NA release in the synaptic cleft, its local uptake and metabolism, the degree of spillover into the circulation and the peripheral plasma clearance of NA. Although the peripheral plasma NA concentra-

Table 3 Effect of placebo, indoramin (mean dose 58 mg), labetalol 150 mg and alinidine 80 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. Means $\pm$ s.e. mean are indicated.

	0 h	2 h	4 h	Na ⁺
Placebo	1.21 $\pm$ 0.23	1.28 $\pm$ 0.32	1.19 $\pm$ 0.25	126.2 $\pm$ 17.2
Indoramin	0.85 $\pm$ 0.20	1.93 $\pm$ 0.84 $\dagger$	1.13 $\pm$ 0.24	171.0 $\pm$ 28.7
Labetalol	1.05 $\pm$ 0.24	1.36 $\pm$ 0.41	1.06 $\pm$ 0.36	124.0 $\pm$ 13.0
Alinidine	1.29 $\pm$ 0.16	2.32 $\pm$ 0.44* $\dagger$	1.90 $\pm$ 0.32	121.8 $\pm$ 20.2

* $P < 0.05$ when compared to placebo. $\dagger = P < 0.05$ when compared to the pretreatment value

tion is the resultant of many variables, the levels may still reflect sympathetic activity (Christensen & Brandsborg, 1973; Lake *et al.*, 1976; Saar & Gordon, 1979; Watson *et al.*, 1979). In the present study, plasma NA concentration was increased after indoramin administration. The increase in plasma NA concentration reflects the enhanced sympathetic activity in response to the fall of arterial pressure, although the increase in peripheral plasma NA concentration may be limited by selective α_1 -adrenoceptor blockade (Nicholls *et al.*, 1984). In the present study, small increases in plasma NA concentration were observed after labetalol administration. In previous studies in normal man (Richards *et al.*, 1979) and in hypertensive patients (Christensen *et al.*, 1978; Carlsen *et al.*, 1980; Dunn *et al.*, 1983), labetalol has been shown to increase plasma NA concentrations. Labetalol inhibits neuronal uptake₁ of NA (Summers & Tillman, 1977; Doggrell & Paton, 1978a; Gulati *et al.*, 1980), although this effect may only be observed at high drug concentrations (Drew *et al.*, 1978). Labetalol also enhances the intra-neuronal release of NA from storage vesicles (Doggrell & Paton, 1978b; Drew *et al.*, 1979). In addition, increased plasma NA concentrations are observed after β -adrenoceptor blockade (Lijnen *et al.*, 1979), possibly due to reduced peripheral NA clearance (Cryer *et al.*, 1979). Plasma NA concentrations may be increased after labetalol administration by any or all of these mechanisms.

In the present study, alinidine produced small reductions of plasma NA concentration in the supine and standing positions, in contrast to the increases observed after indoramin and labetalol. In a previous study, plasma NA concentrations before and after supine exercise in normal man were unchanged after the intravenous administration of alinidine 0.5 mg kg⁻¹ (Stanek *et al.*, 1983). However, in the study of Stanek *et al.* (1983), plasma NA concentration did not increase with exercise, which is not the usual response, and therefore interpretation of their results is difficult (Häggendal *et al.*, 1970; Christensen & Brandsborg, 1973; Johnson *et al.*, 1977; Hagberg *et al.*, 1979).

The reason for the observed reduction of plasma NA concentration after alinidine administration is unclear. Alinidine is metabolised in man to clonidine (Harron *et al.*, 1982b), and clonidine reduces peripheral plasma NA concentrations due to a central reduction in sympathetic outflow (Wing *et al.*, 1977; Dargie *et al.*, 1977; Metz *et al.*, 1978; Mitchell & Pettinger, 1981; Chernow *et al.*, 1983). We consider it unlikely that clonidine is responsible for the changes observed after alinidine, as peak

concentrations of clonidine in plasma are not found until 8 h after the oral administration of alinidine (Harron *et al.*, 1982b) whereas in this study the effects of alinidine on heart rate, arterial pressure and plasma NA concentration were observed within 2 h of drug administration. In addition, the plasma concentration of clonidine observed after single dose administration of alinidine 40 mg (0.26 ± 0.06 mg ml⁻¹) (Harron *et al.*, 1982b) is clearly below the therapeutic range of 1.0–2.0 ng ml⁻¹ (Davies *et al.*, 1977). Although higher levels of clonidine might be expected after alinidine 80 mg, we consider it unlikely that they would be within the therapeutic range. It is possible that alinidine itself may have a central action, but evidence of this has not been found (Kobinger *et al.*, 1982b; Auböck *et al.*, 1982). Another explanation for the possible effect of alinidine on plasma NA concentration would be an effect on NA uptake or metabolism, but concentrations of alinidine within the therapeutic range do not change the output of [³H]-NA from the stimulated guinea pig portal vein (O'Connor, unpublished observations), and so alinidine does not appear to modify transmitter release.

In addition to the effects on plasma NA concentration described above, the three drugs produced different effects on PRA. Indoramin produced a small increase in PRA, similar to that observed in previous studies in normal man (Nicholls *et al.*, 1981, 1984). In hypertensive patients, indoramin produced a small decrease in PRA (Stokes *et al.*, 1979). Administration of labetalol produces either no net change in PRA (Mehta & Cohn, 1977; Frishman *et al.*, 1981), or a reduction (Weidmann *et al.*, 1978; Dawson *et al.*, 1979). In the present study, PRA was unchanged after labetalol administration. Alinidine produced a significant increase in PRA, despite reduced plasma NA concentrations. This is similar to the effects of clonidine (Wing *et al.*, 1977), and may reflect local alterations in renal haemodynamics.

All three drugs reduce arterial pressure in normal man, but their effects on sympathetic activity differ, and this probably reflects their different modes of action. Indoramin produced an increase in plasma NA concentration and a small increase in heart rate and PRA, compatible with vasodilatation due to α -adrenoceptor blockade. Labetalol reduced heart rate, with a small increase in plasma NA concentration and no change in PRA, which is compatible with combined α - and β -adrenoceptor blockade, with possible additional effects on NA metabolism. Alinidine produced small reductions in heart rate, arterial pressure and plasma NA concentration, and an increase in

PRA. As yet, this pattern of response cannot be explained in terms of the known pharmacology of alinidine, and would suggest the possibility that alinidine may reduce arterial pressure by a reduction of sympathetic activity.

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