CARDIOVASCULAR EFFECTS OF INDORAMIN IN MAN— A DOSE RANGING STUDY

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- 1 The effect of single and repeated oral doses of indoramin 25 mg, 50 mg, 100 mg and placebo on arterial pressure and heart rate supine, standing and following immersion of the hand in ice was studied in five normal volunteers.
- 2 Each study period lasted 4 days. Observations were made before and at 2 and 4 h after drug administration on days 1 and 4. On days 2 and 3, the drugs were administered daily, but no observations were made.
- 3 Indoramin did not change arterial pressure or heart rate in the supine position.
- 4 Indoramin did not reduce the cold pressor response.
- 5 Indoramin 25 mg produced small reductions in arterial pressure in the standing position, with no change in heart rate.
- 6 Indoramin 50 mg reduced systolic arterial pressure in the standing position on day 1 from 106.4 ± 2.6 mm Hg (mean $\pm$ s.e. mean) to 88.4 ± 7.4 mm Hg at 2 h ($P < 0.05$ when compared to placebo) and to 96.8 ± 2.2 mm Hg at 4 h ($P < 0.05$); diastolic pressure was reduced from 76.4 ± 4.1 mm Hg to 57.2 ± 6.4 mm Hg at 2 h ($P < 0.01$) and to 64.4 ± 4.3 mm Hg at 4 h ($P < 0.05$). The reductions in arterial pressure were accompanied by an increase in heart rate from 94.0 ± 4.5 beats min^{-1} to 102.0 ± 7.0 beats min^{-1} at 2 h, and to 104.6 ± 8.1 beats min^{-1} at 4 h ($P < 0.05$ when compared to placebo, but not when compared to the pre-treatment value). Similar changes were observed on day 4 after 50 mg indoramin, but the maximum reduction in arterial pressure was observed at 2 h on day 1, and 4 h on day 4.
- 7 Indoramin 100 mg reduced systolic arterial pressure in the standing position on day 1 from 114.0 ± 2.6 mm Hg to 99.2 ± 5.8 mm Hg at 2 h, and to 88.0 ± 5.9 mm Hg at 4 h ($P < 0.01$); diastolic pressure was reduced from 80.4 ± 3.4 mm Hg to 64.4 ± 3.2 mm Hg at 2 h ($P < 0.05$), and to 64.0 ± 4.5 mm Hg at 4 h ($P < 0.05$). The reduction in arterial pressure was accompanied by a small increase in heart rate from 102.2 ± 8.3 beats min^{-1} to 107.2 ± 12.7 beats min^{-1} at 2 h ($P < 0.05$ when compared to placebo, but not when compared to the pre-treatment value); no change in heart rate was observed at 4 h. The changes in arterial pressure and heart rate observed on day 4 after 100 mg indoramin were less than those observed on day 1, but these differences were not significant.
- 8 Indoramin reduces arterial pressure in normal man, but it is not possible to describe a dose-response relationship for the reduction. The reduction is accompanied by only a small increase in heart rate, possibly due to a direct bradycardic action of indoramin on the heart.

Introduction

Indoramin is a selective post-synaptic α_1 -adrenoceptor antagonist (Algate & Waterfall, 1978; Rhodes & Waterfall, 1978). Animal studies have shown that indoramin reduces arterial pressure without producing a reflex tachycardia (Alps *et al.*, 1972a; Baum *et al.*, 1973; Oates *et al.*, 1977). This pattern of response is different from that observed after directly acting vasodilators such as hydralazine or diazoxide, when the fall in arterial pressure is accompanied by an increase in heart rate (Oates *et al.*, 1977). In normal man, indoramin does not change arterial pressure or heart rate in the supine position (Boakes *et al.*, 1972;

Royds *et al.*, 1972; Coltart, 1981; Nicholls *et al.*, 1981). Arterial pressure in the standing position is reduced but is accompanied by only a small increase in heart rate (Coltart, 1981; Nicholls *et al.*, 1981). Following chronic dosing with indoramin in patients with hypertension, arterial pressure is reduced in the standing position, and heart rate is unchanged (Kramer *et al.*, 1974; Gould *et al.*, 1981) or reduced (Carballo *et al.*, 1974; Faerchtein *et al.*, 1976).

Previous studies have indicated that 40 mg indoramin produces a greater fall in standing arterial pressure than 20 mg indoramin (Coltart, 1981). We

wished to know if indoramin reduces arterial pressure in a dose-dependent manner, and, if so, whether the heart rate response also changes with different doses. In the present study we have compared the effect of 25 mg, 50 mg and 100 mg of indoramin and placebo on arterial pressure and heart rate in healthy volunteers.

Methods

Observations were made on five healthy male volunteers aged 18–23 years, mean weight 72.7 ± 2.2 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, Belfast. Subjects were asked to take their normal breakfast on each study day.

Each study period lasted 4 days. Indoramin 25 mg, 50 mg or 100 mg or placebo tablets were administered at weekly intervals. The drugs were administered single (observer) blind and in random order, except that 100 mg indoramin was not given as the first dose of active drug. On days 1 and 4 of each study period, a single dose of the drug was administered at 09.00 h. Observations were made before and at 2 and 4 h after drug administration. On days 2 and 3, the same dose of the drug was taken once daily at 09.00 h, but no measurements were made. At each observation time, subjects were supine for 15 min, and then placed one hand to the wrist into a box containing crushed ice at 0°C , for 60 s. Following a further period of 15 min supine rest, the subjects sat upright for 1 min and then stood for 3 min. Heart rate and arterial pressure were recorded at the end of both periods in the supine position, at the end of the 60 s period of immersion of the hand in ice (the hand being kept in the ice whilst

the observations were made) and at the end of 3 min standing. Heart rate was measured from lead I of a direct reading electrocardiograph, 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 administration.

Results

There was no change in arterial pressure or heart rate in the supine position at 2 h and 4 h after placebo administration on days 1 and 4, when compared to pre-treatment values. The three doses of indoramin did not change arterial pressure or heart rate in the supine position, when compared to placebo on days 1 and 4. Figure 1 shows the changes in arterial pressure during immersion of the hand in ice on day 1; the changes observed on day 4 were similar. Systolic and diastolic arterial pressure increased significantly after immersion of the hand in ice (cold pressor response) before, and 2 and 4 h after placebo. Similar increases in systolic and diastolic arterial pressure in response to ice immersion occurred after the three doses of indoramin. Heart rate was consistently increased by up to 15 beats min^{-1} following immersion of the hand in ice, but these values were not significantly greater when compared to the values prior to immersion of the hand. The heart rate response to cold was not changed by indoramin.

There was no change in arterial pressure in the

Figure 1 Cold pressor test. Effect of placebo and of indoramin 25 mg, 50 mg and 100 mg on systolic and diastolic arterial pressure (mmHg) in the supine position before (●) and after (●—●) immersion of the hand in ice at 0°C for 60 s. Mean $\pm$ s.e. mean have been indicated ($n = 5$).

Table 1 Effect of placebo, indoramin 25 mg, indoramin 50 mg and indoramin 100 mg on systolic and diastolic arterial pressure (mm Hg) and heart rate (beats min⁻¹) in the standing position. Results are the mean ($\pm$ s.e. mean) of observations in five subjects...

Treatment	Day 1			Day 4		
	0	2	4	0	2	4
Placebo	Systolic	113.6 $\pm$ 7.6	105.6 $\pm$ 5.8	114.0 $\pm$ 6.7	102.2 $\pm$ 4.7	108.8 $\pm$ 6.0
	Diastolic	79.6 $\pm$ 6.2	78.4 $\pm$ 3.7	77.2 $\pm$ 6.1	78.6 $\pm$ 3.3	79.2 $\pm$ 4.2
	Heart rate	97.4 $\pm$ 7.7	90.0 $\pm$ 8.1	88.8 $\pm$ 5.3	87.2 $\pm$ 10.6 [†]	97.4 $\pm$ 6.1
Indoramin 25 mg	Systolic	108.8 $\pm$ 7.0	104.4 $\pm$ 5.4	98.4 $\pm$ 2.7*	104.8 $\pm$ 8.6	98.0 $\pm$ 4.9
	Diastolic	77.2 $\pm$ 2.6	69.6 $\pm$ 2.6	72.0 $\pm$ 0.9	76.0 $\pm$ 4.1	65.2 $\pm$ 5.2*
	Heart rate	99.4 $\pm$ 5.8	97.4 $\pm$ 5.6	103.0 $\pm$ 2.1	98.8 $\pm$ 1.5	105.4 $\pm$ 5.0
Indoramin 50 mg	Systolic	106.4 $\pm$ 2.6	88.4 $\pm$ 7.4*	96.8 $\pm$ 2.2*	103.2 $\pm$ 2.6	92.8 $\pm$ 2.9*
	Diastolic	76.4 $\pm$ 4.1	57.2 $\pm$ 6.4**	64.4 $\pm$ 4.3*	70.4 $\pm$ 2.6	62.8 $\pm$ 3.9*
	Heart rate	94.0 $\pm$ 4.5	102.0 $\pm$ 7.0	104.6 $\pm$ 8.1*	98.2 $\pm$ 8.2	102.6 $\pm$ 10.6
Indoramin 100 mg	Systolic	114.0 $\pm$ 2.6	99.2 $\pm$ 5.8	88.0 $\pm$ 5.9**	100.4 $\pm$ 8.6	96.8 $\pm$ 3.3
	Diastolic	80.4 $\pm$ 3.4	64.4 $\pm$ 3.2*	64.0 $\pm$ 4.5*	72.4 $\pm$ 8.3	67.6 $\pm$ 3.7*
	Heart rate	102.2 $\pm$ 8.3	107.2 $\pm$ 12.7*	102.0 $\pm$ 8.9	103.8 $\pm$ 10.5*	96.0 $\pm$ 9.7

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

standing position 2 and 4 h after placebo administration on days 1 and 4 (Table 1). On day 1, 25 mg indoramin reduced systolic arterial pressure at 4 h, with no change in diastolic pressure; this reduction was significant when compared to placebo ($P < 0.05$). On day 4, systolic arterial pressure was significantly lower than the placebo value prior to administration of 25 mg indoramin ($P < 0.05$). There was no obvious reason for this reduction. Indoramin 25 mg produced a small reduction in diastolic pressure at 4 h, which was significant when compared to placebo ($P < 0.05$), but not when compared to the pre-treatment value. On day 1, 50 mg indoramin reduced arterial pressure at 2 h ($P < 0.05$, systolic; $P < 0.01$ diastolic) and at 4 h ($P < 0.05$, systolic and diastolic); the maximum effect was observed at 2 h. On day 4, 50 mg indoramin produced small reductions in arterial pressure at 2 h, and significant reductions at 4 h ($P < 0.05$, systolic and diastolic). The maximum reduction in arterial pressure produced by 50 mg indoramin occurred later on day 4 than on day 1. On day 1, 100 mg indoramin reduced diastolic pressure at 2 h ($P < 0.05$), and systolic ($P < 0.01$) and diastolic ($P < 0.05$) pressure at 4 h; the maximum effect was observed at 4 h. On day 4, 100 mg indoramin reduced systolic and diastolic pressure at 2 and 4 h, but only the reduction in diastolic pressure at 4 h was significant ($P < 0.05$) when compared to placebo. The reductions in systolic and diastolic arterial pressure after 100 mg indoramin were greater on day 1 than on day 4, but these differences were not significant.

Following placebo administration, the heart rate in the standing position (Table 1) was less than the pre-treatment value at 2 and 4 h on both days 1 and 4, and this difference was significant ($P < 0.05$) at 2 h on day 4. Indoramin 25 mg produced no significant changes in heart rate. Indoramin 50 mg produced small increases in heart rate on day 1, but no changes on day 4. On day 1, the value at 4 h was significantly greater than placebo ($P < 0.05$), but was not significantly greater than the pre-treatment value. Indoramin 100 mg produced small increases in heart rate at 2 h on days 1 and 4, which preceded the maximum fall in arterial pressure. These increases were significant when compared to placebo ($P < 0.05$) but not when compared to the pre-treatment values.

No side effects were reported with placebo administration. After 25 mg indoramin, two subjects reported a blocked nose, and three reported no side effects. Four subjects noted side effects after 50 mg indoramin. Three felt faint when standing 2 h after drug administration on day 1, but not on day 4. The dizziness was accompanied by a marked fall in arterial pressure, but loss of consciousness did not occur. In two of the three subjects, the heart rate was higher than the pre-treatment value, and in one, it was less. Other reported side effects were tiredness in two subjects, blocked nose in one and a metallic taste

in one. All the subjects reported side effects after 100 mg indoramin. One subject felt faint when standing 2 h after drug administration on day 1, and again on day 4. Four subjects felt tired. One subject noted a dry mouth and a blocked nose, and another noted that the ice felt colder.

Discussion

Immersion of the hand in ice produces a reflex peripheral vasoconstriction mediated mainly by α -adrenoceptors, resulting in an increase in diastolic arterial pressure, a lesser increase in systolic arterial pressure, and a small increase in heart rate and cardiac output (Taylor, 1981). The cold pressor test is reproducible within an individual (Hines & Brown, 1936).

The degree of arterial pressure increase is inversely related to the temperature of the ice (Taylor *et al.*, 1980), and does not depend on the area of skin involved. It might be expected that α -adrenoceptor blockade would reduce the cold pressor response, but neither phentolamine (Richards *et al.*, 1978) nor prazosin (Dargie *et al.*, 1978; Mancia *et al.*, 1980; Pitterman *et al.*, 1981) reduce the response, but it was reduced by combined α - and β -adrenoceptor blockade with labetalol (Maconochie *et al.*, 1977). Our results confirm the observation that α -adrenoceptor blockade alone does not reduce the cold pressor response.

In the present study, indoramin reduced arterial pressure in the standing position, with only a small increase in heart rate, which confirms previous observations in normal man (Coltart, 1981; Nicholls *et al.*, 1981). The effect of 50 mg indoramin on arterial pressure and heart rate was greater than that of 25 mg, but the effect of 100 mg was the same as 50 mg. Consequently, it is not possible to describe a dose-response relationship for the effect of indoramin on arterial pressure or heart rate. The effect of 50 mg indoramin was similar to the effect of 40 mg described in a previous study (Coltart, 1981). The reduction in arterial pressure produced by indoramin was accompanied by a small increase in heart rate. In contrast, reduction of arterial pressure by directly acting vasodilators (such as hydralazine) or non-selective α -adrenoceptor blocking drugs (such as phentolamine) produces a marked increase in heart rate, which is thought to arise from increased sympathetic activity due to baroreceptor stimulation (Taylor *et al.*, 1965; Koch-Weser, 1976).

There is no obvious reason for the relative lack of tachycardia after indoramin administration. Indoramin does not produce β -adrenoceptor blockade, and does not affect cholinergic activity (Alps *et al.*, 1972b). It has been suggested that a central action may contribute to the observed effects of indoramin

(Elliott, 1976; Gulati *et al.*, 1978), but this action is not thought to be important at therapeutic doses (Baum & Shropshire, 1975) and critical flicker frequency in man is unchanged (Coltart, 1981).

Indoramin has potent local anaesthetic activity (Alps *et al.*, 1971), and some of its cardiovascular effects in the pithed rat resemble those of lignocaine and procaine (Algate *et al.*, 1981). Indoramin reduces $V_{\max}$ of depolarisation in canine isolated myocardial strips (Coltart *et al.*, 1971) which would indicate class I anti-arrhythmic activity. However, our own studies on the anaesthetised dog (Harron, unpublished observations) indicate that indoramin and mexiletine (a class I anti-arrhythmic drug) have different cardiovascular effects. Indoramin reduces arterial pressure and heart rate in a dose-dependent manner, whereas mexiletine up to 4 mg kg⁻¹ has no effect on arterial pressure or heart rate. Both drugs failed to inhibit the tachycardia produced by stellate ganglion stimulation. The fall in heart rate produced by indoramin may therefore not be related to its known local anaesthetic (membrane stabilising) activity. Heart rate may also be reduced by a direct action on the sino-atrial node. Drugs which are thought to act in this way include alinidine (Kobinger *et al.*, 1979) and bepridil (Cosnier *et al.*, 1977; Beaughard *et al.*, 1982). Alinidine may act by slowing diastolic depolarisation and thus causing bradycardia directly, which has been described as a class V anti-arrhythmic action (Millar & Vaughan Williams, 1981). The monophasic action potentials observed after indoramin administration resemble class I rather than class V anti-arrhythmic activity. It is possible that indoramin may exert a direct bradycardic effect on the heart, which cannot be explained in terms of anion antagonism (Class V activity).

The presence of myocardial α -adrenoceptors has been demonstrated *in vitro* in rat ventricular strips (Wenzel & Su, 1966), guinea-pig atria (Govier, 1967), and rabbit atria (Benfey & Varma, 1967), and also *in vivo* in the anaesthetised dog (Garvey, 1969). These α -adrenoceptors when stimulated produced positive inotropic (Govier, 1967) and possibly positive chronotropic effects (James *et al.*, 1968). The presence of myocardial postsynaptic α_1 - and presynaptic α_2 -adrenoceptors has been confirmed by radioligand binding (Guicheney *et al.*, 1978; Karliner *et al.*, 1979). Recently the presence of α -adrenoceptors has been demonstrated in human atrial preparations (Schümann *et al.*, 1978). Stimulation of these receptors at a physiological frequency (1 Hz) produced a positive inotropic effect, but no change in heart rate. Blockade of these receptors by indoramin could therefore produce a negative inotropic effect, which has been demonstrated in animal preparations (Alps *et al.*, 1972b) but not in normal man (Coltart, 1981). The physiological role of myocardial α -adrenoceptors in the regulation of heart rate in man is

as yet unclear.

Another explanation that has been advanced for the relative lack of tachycardia after indoramin administration is differential α -adrenoceptor blockade. Indoramin is more active at post-synaptic α_1 -than presynaptic α_2 -adrenoceptors (Algate & Waterfall, 1978; Rhodes & Waterfall, 1978). Prazosin is also relatively selective for α_1 -adrenoceptors (Cambridge *et al.*, 1977; Caverio *et al.*, 1977; Graham & Pettinger, 1979). Following chronic administration, both drugs reduce arterial pressure with only a small increase in heart rate, and it is thought that failure to block pre-synaptic α_2 -adrenoceptors allows the negative feedback inhibition of noradrenaline release to continue, so reducing the amount of noradrenaline available to stimulate myocardial β_1 -adrenoceptors (Langer, 1977; Yamaguchi *et al.*, 1977; Graham & Pettinger, 1979). The extent to which pre-synaptic α_2 -adrenoceptor blockade modulates the heart rate response may be limited (Drew, 1980; Reid & Hamilton, 1980) and it has proved difficult to demonstrate differential α -adrenoceptor blockade in man (Mulvihill-Wilson *et al.*, 1979; FitzGerald *et al.*,

1981). In the anaesthetised rat (Oates *et al.*, 1977), indoramin and prazosin reduced arterial pressure and reduced heart rate, unlike hydralazine and diazoxide, which reduced arterial pressure but increased heart rate. The effects of prazosin were opposed by phentolamine or pentolinium, whereas the heart rate response to indoramin remained intact. If the effect of indoramin and prazosin on heart rate was due to the same mechanism (differential α -adrenoceptor blockade), phentolamine and pentolinium would have produced a similar response. This would suggest that the bradycardia following the reduction of arterial pressure by indoramin and prazosin may have been due to different mechanisms.

Our results confirm that indoramin reduces arterial pressure in man, and that the reduction is accompanied by only a small increase in heart rate. The reason for the relative lack of tachycardia after indoramin administration remains unclear, but it may be due to a direct bradycardic action of indoramin.

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