EVALUATION OF INDORAMIN ADDED TO OXPRENOLOL AND BENDROFLUAZIDE AS A THIRD AGENT IN SEVERE HYPERTENSION

A.J. MARSHALL, M.A. KETTLE & D.W. BARRITT

Department of Cardiology, Bristol Royal Infirmary, Bristol BS2 8HW

- 1 Indoramin, an α -adrenoceptor blocking agent has been given as a third agent to patients with severe hypertension treated with adequate doses of a β -adrenoceptor blocking drug and a thiazide diuretic.
- 2 A further fall in blood pressure followed the addition of indoramin. With 75 mg twice daily this was on average a fall of 12% of mean arterial pressure in the supine position, 16% standing and 17% after exercise.
- 3 The rise in blood pressure caused by isometric exercise was not altered by indoramin.
- 4 Indoramin slowed the heart rate. On 75 mg twice daily the reduction was 14% at rest and 19% after exercise.
- 5 Side effects of indoramin were sedation, sleep disturbance and vivid dreams.

Introduction

The usual first choice treatment for raised blood pressure is either a thiazide diuretic or a beta adrenoceptor blocking drug (Beilin, Bulpitt, Coles, Dollery, Gear, Harper, Johnson, Munro-Faure & Turner, 1980). If the fall in pressure achieved with either given alone is inadequate then, where there is no specific contra-indication, the two should be given together (Petrie, Galloway, Webster, Simpson & Lewis, 1975; Marshall, Barritt, Pocock & Heaton, 1977). However, patients with severe hypertension may require more than two agents and the choice of drug to be next added to a diuretic and β -adrenoceptor blocking drug is still debated.

Indoramin (Wy 21901, Figure 1) is one of a series of benzamidopiperidyl-ethylindoles and is a post junctional α -adrenoceptor blocking drug (Alps, Hill, Johnson & Wilson, 1972; Variava & Turner, 1973; Rhodes & Waterfall, 1978). In addition it has been shown to have cardioinhibitory properties, a local anaesthetic action and it blocks histamine and 5-hydroxytryptamine receptors (Alps *et al.*, 1972; Collis & Alps, 1973). The pharmacokinetics of indoramin have been studied in man (Draffan, Lewis, Firmin, Jordan & Dollery, 1976).

Preliminary clinical studies of indoramin indicated that it might have a useful hypotensive action (Royds, 1972.) Further trials have established its potential when given alone to hypertensive patients (Lewis, George & Dollery, 1973; White, Royds & Turner, 1974; Faerchtein, Roque, Kastansky,

Molecular formula $C_{22}H_{25}N_3O.HCl$

Molecular weight 383.9

Figure 1 Structural formula of indoramin

Campos & Puppin, 1976). We wished to assess the effectiveness, tolerability and safety of indoramin when given with a diuretic and a β -adrenoceptor blocking drug to patients with severe hypertension.

Methods

Patients

Severely hypertensive patients, whose response to a combination of oxprenolol and bendroflumazide was inadequate, were entered into the study. At entry to the trial each patient had taken 160 mg oxprenolol twice daily and 5 mg bendroflumazide daily for at least 6 weeks. On these doses the supine systolic blood

pressure ranged from 174–246 (average 212 mmHg) and diastolic pressure from 107–149 (average 129 mmHg). No patient had evidence of accelerated hypertension or heart disease.

Clinical trial

The nature of the trial was explained to all the patients and they gave written consent to participate. All were outpatients and they attended a clinic specifically set aside for the study. They were seen at 2 weekly intervals throughout the trial and appointments were at the same time of the day.

Blood pressure and heart rate measurements were made by the same observer throughout. All blood pressure measurements were made with the London School of Hygiene and Tropical Medicine Sphygmomanometer (Rose Box) in order to reduce observer bias. The diastolic pressure was recorded at Phase V.

Measurements were made after 5 min rest, supine, after 1 min standing, after 1 min of two step exercise and at minute intervals for 3 min of static muscular exercise. (A standardised handgrip test at 30% maximum voluntary contraction was used.) During this isometric exercise only the change in systolic pressure was recorded.

Treatment

Active and placebo tablets were identical so that the assessment of indoramin was single (patient) blind. During the first two fortnight periods placebo tablets were given in addition to oxprenolol 160 mg twice daily and 5 mg bendrofluazide a day. Next 50 mg indoramin twice a day was given with oxprenolol and bendrofluazide for 4 weeks. Placebo tablets were then substituted for active indoramin for a 2 week washout period. Then the dose of indoramin was increased to 75 mg twice daily for 4 weeks. Finally oxprenolol was stopped, placebo tablets substituted and indoramin 75 mg twice daily given with 5 mg of bendrofluazide daily for 2 weeks. All tablets were dispensed in the blood pressure clinic. Every fortnight three pots containing the appropriate number plus three extra tablets were given to each patient. We asked for the pots to be returned at the next visit.

Side effects

At every attendance the patients were given a questionnaire to complete and return at the next visit. They were asked to volunteer side effects and to mark any of 27 specific complaints noted in the 2 week treatment period. A full blood count, liver function tests, urea and electrolytes and urine analysis were performed at each visit.

Statistical analysis

The analyses were done using the paired Students' *t*-test.

Results

Two patients, a man and a woman, withdrew from the study. Both complained of feeling intolerably lethargic. One described this symptom during the run in period and the other during the first indoramin treatment period. Both refused to continue in the trial. Ten patients completed all treatment periods and their results are analysed.

Eight were men and two women. They were aged between 32 and 60 years (average 53 years).

Blood pressure

Effect of adding indoramin The addition of both 50 mg indoramin twice daily and 75 mg indoramin twice daily to β -adrenoceptor blockade and thiazide diuretic caused a statistically significant reduction in blood pressure (Table 1).

There was a trend for blood pressure to be lower in the placebo washout period compared with the pretreatment period. This difference never reached statistical significance.

Comparison of 50 mg and 75 mg indoramin twice daily The effect of 75 mg indoramin twice a day was greater than that of the smaller dose but apart from the diastolic pressure in the standing position, ($P < 0.025$), the difference was not statistically significant.

Postural and exercise hypotension Blood pressures with oxprenolol and bendrofluazide were similar in the supine, standing and exercise positions. When indoramin was added there were small falls in blood pressure on standing and after exercise. These changes reached statistical significance with 75 mg indoramin twice daily.

Withdrawal of oxprenolol Blood pressure rose after oxprenolol was withdrawn. There was a significant difference between systolic pressure after exercise ($P < 0.005$) and standing and exercise diastolic pressure ($P < 0.05$).

Static muscular exercise Table 2 shows the systolic blood pressure and rise in systolic blood pressure with 3 min of sustained 30% maximum hand grip. The absolute level of blood pressure after the addition of both doses of indoramin to oxprenolol and bendrofluazide was reduced ($P < 0.05$). The

actual rise in blood pressure associated with isometric exercise was not significantly altered by indoramin.

Heart rate

The mean heart rate was similar in the run in and washout periods. There was a fall in exercise heart rate with 50 mg indoramin twice daily ($P < 0.05$).

Indoramin 75 mg twice a day slowed the heart rate in all positions. This change was significant when compared to values in either the run in (Table 3) or washout period.

There was a rise in heart rate when oxprenolol was withdrawn compared to the run in period and the treatment periods when indoramin, bendrofluazide and oxprenolol were given together ($P < 0.005$).

Table 1 Blood pressures (mean $\pm$ (s.d.) mmHg)

Treatment	Placebo, oxprenolol, bendrofluazide	Indoramin 50mg $\times$ 2, oxprenolol, bendrofluazide	Placebo, oxprenolol, bendrofluazide	Indoramin 75mg $\times$ 2, oxprenolol, bendrofluazide	Indoramin 75mg $\times$ 2, placebo, bendrofluazide
Supine	205	187	194	184	196
SBP	(± 23)	(± 30)	(± 30)	(± 27)	(± 30)
DBP	127	118	121	111	115
	(± 13)	(± 14)	(± 16)	(± 12)	(± 12)
Standing	198	178	191	170	182
SBP	(± 31)	(± 36)	(± 38)	(± 36)	(± 36)
DBP	127	115	126	106	113
	(± 16)	(± 16)	(± 17)	(± 14)	(± 17)
Exercise	206	182	196	171	199
SBP	(± 30)	(± 36)	(± 27)	(± 31)	(± 32)
DBP	122	109	120	100	115
	(± 18)	(± 12)	(± 14)	(± 9)	(± 12)
Addition of indoramin					
		50mg $\times$ 2	75mg $\times$ 2		
Supine	SBP	$P = < 0.025$	< 0.01		
	DBP	$P = < 0.05$	< 0.01		
Standing	SBP	$P = < 0.005$	< 0.005		
	DBP	$P = < 0.02$	< 0.001		
Exercise	SBP	$P = \text{N.S.}$	< 0.01		
	DBP	$P = < 0.025$	< 0.005		

Table 2 Isometric exercise and blood pressure (mean $\pm$ (s.d.) mmHg)

<i>Treatment</i>		<i>Systolic BP at 3 min</i>	<i>Rise in BP</i>
Oxprenolol, bendrofluazide	(1) Run in	230 (± 26)	26 ± 11
	(2) Washout	218 (± 31)	25 ± 22
+ Indoramin 50mg × 2		211 (± 37)	27 ± 19
+ Indoramin 75mg × 2		199 (± 37)	17 ± 13
Indoramin 75mg × 2 bendrofluazide		216 (± 34)	21 ± 11

Side effects

Three side effects were volunteered and marked on the list of 27 symptoms more frequently ($P < 0.5$) during indoramin periods. These were tiredness, disturbance of sleep and vivid dreams.

Compliance

No patient missed attendance. Two hundred and nineteen tablet pots were returned (240 were dispensed). On 15 occasions no tablets were left in the pot. The tablet count was correct 182 times. There was no evidence of less compliance to medication in any particular treatment period.

Blood and urine analysis

No abnormalities in the haematological, biochemical and urinary examination were detected during the study.

Discussion

The patients were a consecutive group of severe hypertensives treated with 320 mg oxprenolol and 5 mg bendrofluazide a day. Our previous experience suggests that there is usually little to be gained by increasing the daily dose of either drug (Barritt & Marshall, 1977; Marshall *et al.*, 1977). They required a third agent and indoramin was added. It produced a further fall in blood pressure. The average fall in mean arterial pressure with 75 mg indoramin twice a day was 12% in the supine position, 16% standing and 17% after exercise. There was a fall in pressure on standing with both dose regimes of indoramin. This postural fall was statistically significant with 75 mg indoramin twice daily. At each dose level blood pressure reduction after 2 weeks treatment was not statistically different from that at 4 weeks. The rise in pressure during the placebo washout period confirmed that the incremental effect was indeed due to the addition of indoramin. Like other hypotensive agents indoramin reduced the absolute level of blood

pressure attained during isometric exercise but the rate of rise of pressure due to this stimulus was not altered. There was a trend for the blood pressure to be lower with 75 mg indoramin twice daily compared with 50 mg twice a day but this trial was not designed as a dose response study. The shape of the dose response curve of indoramin remains to be determined.

The reduction in pressure was similar to that which we found with the addition of prazosin, another post junctional α -adrenoceptor blocking agent, to β -adrenoceptor blockade in severe hypertensives (Marshall *et al.*, 1977). Stokes, Frost, Graham & MacCarthy (1979) have also shown that indoramin and prazosin have similar hypotensive potency when added to β -adrenoceptor blockade. Wilcox & Mitchell (1977) studied the contribution of atenolol, bendrofluazide and the vasodilator hydralazine to the management of severe hypertension. Hydralazine 50 mg twice a day added to the other two agents produced a mean reduction in pressure of 6 mmHg. Indoramin is, therefore, likely to be as effective as either prazosin or hydralazine when added to a thiazide diuretic and β -adrenoceptor blocking drug in severe hypertensives. However, in this study of severe hypertensives its additional effect was not sufficient to reduce their blood pressures to a clinically acceptable control level. Thus although the fall in pressure caused by indoramin was significant most clinicians would be unhappy to let these patients maintain the achieved pressures for a long period and would want to substitute or add another hypotensive agent.

Unlike other α -adrenoceptor blockers or vasodilators, indoramin slows the heart rate. Oxprenolol had reduced both heart rate and blood pressure and when it was withdrawn both rose. The addition of indoramin at both doses caused a further fall in heart rate and this reached statistical significance supine, standing and after exercise with 75 mg indoramin twice daily. At this dose there was a reduction of heart rate of 14% at rest and 19% after exercise. This effect may be beneficial in the treatment of angina pectoris and hypertension.

There was a real association between indoramin

Table 3 Heart rate changes (mean ($\pm$ s.d.) beats/min)

Treatment	Placebo, oxprenolol, bendrofluazide	Indoramin 50mg $\times$ 2, oxprenolol, bendrofluazide	P	Placebo, oxprenolol, bendrofluazide	Indoramin 75mg $\times$ 2, oxprenolol, bendrofluazide	P	Indoramin 75mg $\times$ 2, placebo, bendrofluazide
Supine	82 ($\pm$ 11)	76 ($\pm$ 7)	NS	84 ($\pm$ 12)	72 ($\pm$ 7)	< 0.02	98 ($\pm$ 15)
Standing	87 ($\pm$ 12)	80 ($\pm$ 8)	NS	86 ($\pm$ 11)	78 ($\pm$ 8)	< 0.05	105 ($\pm$ 15)
Exercise	109 ($\pm$ 20)	97 ($\pm$ 12)	< 0.05	112 ($\pm$ 22)	91 ($\pm$ 10)	< 0.02	119 ($\pm$ 19)

therapy and excessive sedation, sleep disturbance and vivid dreams. Symptoms of postural hypotension, which can be caused by prazosin both after first dose and chronically, were not a feature of indoramin treatment.

In this relatively small group of patients the efficacy of indoramin in lowering blood pressure is confirmed. It can be safely added to a thiazide diuretic and β -adrenoceptor blocking drug. It is unlikely that larger studies will show it to be more potent as a third agent than the drugs in present use (e.g. methyl dopa, hydralazine and prazosin). Its

place in therapy will depend on the frequency and severity of side effects. A series of ten patients is clearly inadequate either to show all the possible unwanted effects or their frequency. If the sedative effect reported by some of our patients should prove to be common then indoramin's clinical usefulness will be limited.

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