Clinical Evaluation of Indoramin as the Sole Agent for the Treatment of Hypertension

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SUMMARY

An open-ended clinical trial of Indoramin (WY-21901), a new antihypertensive agent with both α-adrenergic blocking and cardio-inhibitory properties, was conducted on a group of 27 patients with mild or moderate essential hypertension. Blood pressures, erect and supine, were effectively lowered. In 70% of the patients the mean standing diastolic pressures were well controlled. Heart rate was not significantly lowered. Side-effects occurred in 80% of patients, but did not persist in most of them. Severe side-effects, necessitating withdrawal of Indoramin, were experienced by one-third of the patients.

Proteinuria was observed in 3 patients and a slightly elevated serum urea in 1. No other biochemical tests were abnormal.

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Indoramin, 3-(2-(4-benzamidopiperid-1-yl)ethyl) indolehydrochloride, (WY-21901), is a new, oral antihypertensive agent. In animals it has been shown to act by competitive α-adrenergic receptor blockade[1] and by reducing the rate and force of myocardial contraction.[1,2] The latter action is thought to be due to a local anaesthetic or lignocaine-like effect on the myocardium. The possibility that Indoramin might simultaneously modify two of the mechanisms involved in blood pressure control, viz. cardiac output and peripheral resistance, led to its investigation in healthy human subjects in whom it lowered blood pressure in the supine and standing positions[2,3] without significantly affecting cardiac output or heart rate.

In this article the efficacy and side-effects of Indoramin as the sole therapeutic agent in the treatment of essential hypertension are reported.

PATIENTS AND METHODS

Twenty-seven patients with essential hypertension were selected from those attending the outpatients' clinic at the Johannesburg General Hospital. (The purpose of the trial was explained to each patient and their informed consent obtained.) The mean age was 61,8 years. Nineteen were females and 8 were males. All antihypertensive therapy was stopped for 2 weeks to establish basal or pretreatment blood pressures (Table I) and pulse rates, and also to determine the severity of hypertension.

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TABLE I. STANDING DIASTOLIC BLOOD PRESSURE, PRETREATMENT, AFTER 2 WEEKS OFF ALL ANTIHYPERTENSIVE THERAPY

Standing diastolic blood pressure (mmHg)	No. of patients
90 - 99	4
100 - 109	6
110 - 119	10
120 - 129	3
>129	4
	27

The severity of hypertension was classified as mild, moderate or severe, according to an index derived from the blood pressure, optic fundi, electrocardiogram, chest X-ray film, urinalysis, serum urea and cerebrovascular history.[4] No patients in this series had severe hypertension by these criteria. Secondary hypertension was excluded by clinical examination, by testing the urine for protein, cells and bacteria (colony count), intravenous pyelography and the measurement of 24-hour urinary vanillylmandelic acid excretion. Serum urea, Na^+, K^+, Cl^-, HCO^-_3, uric acid and random glucose levels were determined. Chest X-ray films and electrocardiograms were taken.

Patients were seen at the same time of the day, by the same investigator, at weekly intervals. At each visit blood pressure and pulse were recorded in the recumbent position after the patient had been supine for at least 3 minutes, and in the standing position 1 minute after rising. (Blood pressures were measured with a Hawksley random zero sphygmomanometer,[5] to minimise observer bias and digit preference.) At each visit, the patients were questioned about headache, dizziness, tiredness, insomnia, palpitations or any other symptoms. Symptoms were graded by the patient as mild, moderate or severe. In the third week Indoramin was started at a dose of 60 mg/day (in 3 divided doses). The dose was progressively increased each week until the blood pressure became stabilised at a satisfactory level (i.e. standing diastolic blood pressure less than 100 mmHg); or until side-effects precluded further increases or warranted withdrawal of the drug. In each case, the trial was terminated after 3 successive weeks of satisfactory blood pressure, or if side-effects prevented

increases in dosage. The mean duration of therapy was 7,9 weeks.

Laboratory Investigations

At the end of the pretreatment and trial periods the following were determined: protein in urine; haemoglobin, packed cell volume, mean corpuscular haemoglobin concentration, white cell count (total and differential); serum urea, sodium, potassium, chloride, bicarbonate, uric acid, serum glutamic oxaloacetic and glutamic pyruvic transaminases, alkaline phosphatase, bilirubin, albumin, globulin; and direct Coombs test.

The assessment of blood pressure control used in this article is that of Athanassiadis *et al*,[6] based on the mean standing diastolic pressure (MSDP) over the final 3 weeks of treatment, as follows:

Good control: MSDP of 100 mmHg or less, or at least 41 mmHg below pretreatment levels.

Fair control: MSDP of 101 - 110 mmHg or 21 - 40 mmHg below pretreatment levels.

Poor control: MSDP of over 110 mmHg but 11 - 20 mmHg below pretreatment levels;

Failed control: MSDP not significantly different from pretreatment levels.

The percentage change in blood pressure and heart rates between the pretreatment and the final values was calculated, and probability (P) was determined from Student's t-tables. Values of P of $>0,05$ were considered not significant.

RESULTS

Dose

The doses administered at the end of the trial are shown in Fig. 1.

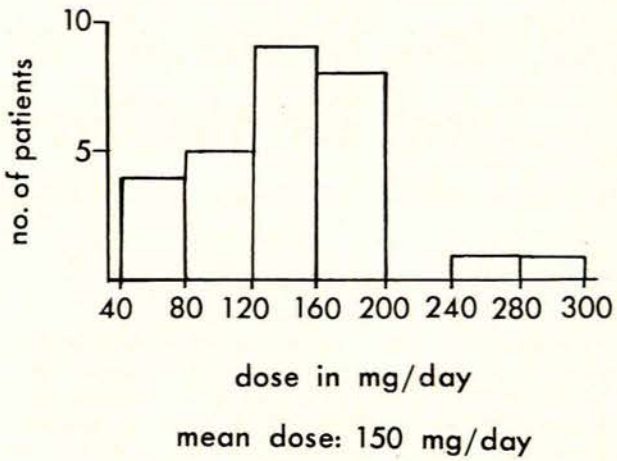

Fig. 1. Final dose of Indoramin (27 patients).

TABLE III. EFFICACY OF INDORAMIN AS THE SOLE AGENT IN THE TREATMENT OF ESSENTIAL HYPERTENSION (27 PATIENTS)

Control of MSDP*	No. of patients	
Good	8	70%
Fair	11	
Poor	0	30%
Failed	8	

* For criteria of control, see text. MSDP = mean standing diastolic pressure.

Control of Blood Pressure

Indoramin was found to lower the mean blood pressure of the group from 200/115 mmHg to 179/103 mmHg supine, and from 185/114 mmHg to 160/99 mmHg standing. Table II shows the mean fall in blood pressure expressed as a percentage of the pretreatment blood pressure. The efficacy of Indoramin in treatment of hypertension is shown in Table III. Thus control of blood pressure was 'good' or 'fair' in 19 of the 27 patients (70%). Table IV shows the mean fall in blood pressure as a percentage in these 19 patients. In 8 patients (30%) control was poor or absent. In 3 of 8 the MSDP rose.

Heart Rate

The mean recumbent heart rate was reduced from 78,3 to 71,1 beats per minute. In 12 patients it was unchanged or rose. In the erect position the mean rate fell from 85,1 to 80,8 beats per minute, being unchanged or elevated in 14 patients. The bradycardia on Indoramin was not statistically significantly different from pretreatment heart rate (Table V).

TABLE II. MEAN FALL IN BLOOD PRESSURE ON INDORAMIN THERAPY (ALL PATIENTS)

	Blood pressure (mmHg)		Percentage fall of blood pressure	Standard error of mean	
	Off therapy	On Indoramin			
Supine BP					
Systolic	**200**	**179**	**8,9**	**3,1**	$P<0,01$
Diastolic	**115**	**103**	**11,3**	**2,7**	$P<0,001$
Standing BP					
Systolic	**185**	**160**	**13,2**	**3,7**	$P<0,005$
Diastolic	**114**	**99**	**11,2**	**2,7**	$P<0,001$

TABLE IV. MEAN FALL IN BLOOD PRESSURE OF PATIENTS WHO RESPONDED TO INDORAMIN

	Blood pressure (mmHg)		Percentage fall of blood pressure	Standard error of mean	
	Off therapy	On Indoramin			
Supine BP					
Systolic	**209**	**177**	**13,3**	**2,3**	$P<0,001$
Diastolic	**119**	**101**	**17,7**	**1,7**	$P<0,001$
Standing BP					
Systolic	**189**	**153**	**17,4**	**2,8**	$P<0,001$
Diastolic	**118**	**96**	**17,6**	**1,6**	$P<0,001$

TABLE V. MEAN FALL IN HEART RATE (PERCENTAGE OF PRETREATMENT VALUE) OF 27 PATIENTS ON INDORAMIN

	Mean percentage fall	Standard error of mean		
Supine	**4,4**	**2,5**	$P<0,1$	**Not significant**
Standing	**2,2**	**2,8**	$P<0,5$	

Side-Effects (Table VI)

Side-effects were reported by 22 patients (80%), but most were occasional or transient. The most common persistent side-effects were tiredness, nasal stuffiness and dry mouth. The most severe side-effect was tiredness. Indoramin had to be stopped in 9 patients (33%) because of severe side-effects (tiredness in 6 patients, dizziness in 2, nasal stuffiness in 3 and impotence which reversed 6 weeks later in 1 patient). Note that in some cases more than one severe side-effect was present. Table VII shows that the side-effects were more or less evenly distributed between the patients who responded to Indoramin and those who did not. Three patients were depressed while on treatment; we were, however, unable to assess whether this was linked to Indoramin or not.

Laboratory Investigations

In 2 patients a trace of protein appeared in the urine; proteinuria had been absent in both in the pre-

TABLE VI. SIDE-EFFECTS OF INDORAMIN THERAPY (27 PATIENTS)

		Severity			Duration	
Side-effect	No. of patients	Mild	Moderate	Severe	Transient or occasional	Persistent
Tiredness	**15**	**2**	**8**	**5**	**9**	**6**
Nasal stuffiness	**9**	**2**	**4**	**3**	**6**	**3**
Dry mouth	**4**	**2**	**1**	**1**	**1**	**3**
Dizziness	**8**	**3**	**4**	**1**	**6**	**2**
Impotence	**1**	**0**	**0**	**1**	**0**	**1**
Insomnia	**3**	**1**	**1**	**1**	**3**	**0**
	40	**10**	**18**	**12**	**25**	**15**

No. of patients with one or more side-effects = 22 = 80%. Indoramin stopped because of side-effects in 9 (33%) patients.

TABLE VII. COMPARISON OF INCIDENCE OF SIDE-EFFECTS BETWEEN PATIENTS WHO RESPONDED TO INDORAMIN ('GOOD' OR 'FAIR' CONTROL) AND THOSE WHO DID NOT RESPOND ('POOR' OR 'FAILED' CONTROL)

	Severity of responders (19 patients)				Severity of non-responders (8 patients)			
Side-effect	No.	Mild	Mod.	Severe	No.	Mild	Mod.	Severe
Tiredness	**10**	**2**	**5**	**3**	**5**	**0**	**3**	**2**
Nasal stuffiness	**7**	**2**	**3**	**2**	**2**	**0**	**1**	**1**
Dry mouth	**1**	**1**	**0**	**0**	**3**	**2**	**0**	**1**
Dizziness	**6**	**2**	**3**	**1**	**2**	**1**	**1**	**0**
Impotence	**1**	**0**	**0**	**1**	**0**	**0**	**0**	**0**
Insomnia	**1**	**0**	**0**	**1**	**2**	**1**	**1**	**0**
	26	**7**	**11**	**8**	**14**	**4**	**6**	**4**

treatment period. One did not respond to Indoramin; his blood pressure had, in fact, risen. The other was a woman with a serum urea of 54 mg/100 ml before and 50 mg/100 ml after treatment with Indoramin. After cessation of therapy the proteinuria disappeared in both. One male developed a '2+' proteinuria, but did not return for follow-up. In 1 woman the serum urea rose from 34 to 50 mg/100 ml. No other biochemical abnormalities were detected in any patient. Haematological and liver function tests remained within normal limits. In no instance was the Coombs test positive.

DISCUSSION

Indoramin was effective in lowering the blood pressure of hypertensive patients, control being good or fair in 70%. Side-effects were observed in 22 of 27 patients studied (80%). The incidence of side-effects would probably have been lower if diuretics or other hypotensive therapy had been added, as is common medical practice.

In order to evaluate this drug fairly, it is desirable to compare it with other antihypertensive agents. However, one should be cautious in comparing drugs from different trials as (*a*) patient groups may not be identical; (*b*) diuretics are often used, allowing a lower dosage of therapeutic agent and hence fewer side-effects; and (*c*) the method of eliciting and scoring side-effects may differ. However, some comparison may be made with alpha-methyldopa, one of the few antihypertensive agents which has been thoroughly documented in this regard.

Efficacy

Johnson *et al.*[7] found that blood pressure control was good or fair in 85 of 100 patients treated with methyldopa for a mean period of 15,7 months, but had to be discontinued in an additional 14 patients. The diuretic chlorthalidone was also administered to 34 of the 100, but the trial included many patients with severe hypertension who might have been excluded from our trial. In 34 patients with benign essential hypertension,[8] treated with methyldopa alone, good or fair control was recorded in 85%.

Side-Effects

It is difficult to compare the precise incidence and severity of side-effects because drugs are somewhat different in action and are tolerated in varying degrees by individual patients. In this study leading questions were used to elicit side-effects, and it is likely that this technique will overestimate the incidence of these side-effects. With this reservation, it is clear that the incidence of side-effects in our trial (80%) is similar to that reported in the study on methyldopa (75% of 114 patients). However, the side-effects were severe enough to necessitate withdrawal of Indoramin in one-third of all our patients, compared with only 17% of those on methyldopa. This may represent a greater severity of side-effects, or may reflect a greater sensitivity to these effects on the part of our patients or investigators, or both. A larger, comparative, study is planned to answer these and similar questions.

It is noteworthy that tachycardia was unusual with Indoramin in contrast to other α-adrenoceptor blocking agents.

The reversible proteinuria found in 3 patients and the slightly raised serum urea in 1, may be due to the drug, or may be part of the natural history of hypertensive renal disease, or be unrelated to both. At this stage in the assessment of this drug it seems wise, however, to suggest that renal failure may be a contra-indication to the use of Indoramin, and to suggest that urinalysis and serum urea estimations be performed frequently during its use.

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REFERENCES

1. Alps, B. J., Borrows, E. T., Johnson, E. S., Staniforth, M. W. and Wilson, A. B. (1972): Cardiovasc. Res., **6**, 226.
2. Coltart, D. J., Lockhart, J. D. F., Royds, R. B. and Turner, P. (1971): Brit. J. Pharmacol., **43**, 467.
3. Royds, R. B., Coltart, D. J. and Lockhart, J. D. F. (1972): Clin. Pharmacol. Ther., **13**, 380.
4. Veterans Administration Cooperative Study on Antihypertensive Agents (1960): Arch. Intern. Med., **106**, 81.
5. Wright, B. M. and Dore, C. F. (1970): Lancet, **1**, 337.
6. Athanassiadis, D., Cranston, W. I., Juel-Jensen, B. E. and Oliver, D. O. (1966): Brit. Med. J., **2**, 732.
7. Johnson, P., Kitchin, A. H., Lowther, C. P. and Turner, R. W. D. (1966): *Ibid.*, **1**, 133.
8. Hamilton, M. and Kopelman, H. (1963): *Ibid.*, **1**, 151.