Indoramin in the treatment of pregnancy hypertension

A placebo-controlled trial comparing the efficacy of indoramin with alpha-methyldopa

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Summary

A placebo-controlled trial was used to assess the antihypertensive efficacy of indoramin in the management of pregnancy hypertension. Sixty patients were recruited into the study and only 17 attained satisfactory blood pressure control. In the doses of drugs administered indoramin was not shown to be more effective than alpha-methyldopa.

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The use of antihypertensive agents in pregnancy hypertension is controversial, since treatment is primarily directed to the control of one of the manifestations and not to the disease itself. Severe hypertension, however, may be a risk to the mother and necessitate treatment. When hypertension is severe and the fetus is immature it may be possible to 'buy time' with antihypertensive therapy and allow the fetus to attain maturity and be safely delivered. The choice of antihypertensive drug in pregnancy depends on the mechanism of action of the drug used, its efficacy and its possible effects of the fetus. The ideal antihypertensive should reduce peripheral resistance but not impair maternal cardiac output and should not reduce uterine perfusion. If peripheral vasodilatation is disproportionately greater than the vasodilatation of the uterine vessels this may reduce uterine blood flow and produce fetal hypoxia. An ideal agent should not only lower blood pressure but should also preferentially vasodilate the uterine circulation and increase uterine blood flow.

The number of placebo-controlled clinical trials has been relatively few[1-6] and the ability of many antihypertensive agents to produce a sustained fall of blood pressure, particularly in severe hypertension, remains to be demonstrated. Furthermore, many drugs have been used in the treatment of pregnancy hypertension but none have been shown to improve choriodecidual perfusion and fetal benefits have been marginal. Some antihypertensive drugs have significant side-effects on the mother or produce deleterious effects on the fetus, which may limit their use.

Indoramin is a selective α_1-postsynaptic adrenergic antagonist with membrane-stabilising properties, and it has been shown to be of value in the treatment of non-pregnant hypertensive patients. It produces vasodilatation without impairing cardiac output[7,8] and theoretically, is a potentially good drug for the treatment of hypertension in pregnancy. A randomised controlled clinical trial was carried out to compare the effects of indoramin with those of an established antihypertensive drug, alpha-methyldopa, and those of a placebo.

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Patients and methods

Black and coloured patients between 28 weeks' and 36 weeks' gestation attending the Pregnancy Hypertension Clinic at Groote Schuur Hospital were recruited into the study after informed consent about the nature and purpose of the trial had been obtained. All patients were admitted for preliminary assessment and were only entered into the trial if their mean 24-hour diastolic blood pressure after admission was in the range 100 - 120 mmHg with or without proteinuria.

Patients were allocated to one of three treatment groups (indoramin, methyldopa or placebo) using a randomised block design in which the patients were divided into 1 of 4 patient categories: primigravid or multigravid, and proteinuric or non-proteinuric. This design was used to reduce the possible confounding effect of difference in the nature and the severity of the underlying disease on the response to treatment. The trial was conducted in three phases.

Phase I

Patients were randomly allocated to indoramin 50 mg twice daily or alpha-methyldopa 1 g twice daily or placebo 1 tablet daily. The patients remained in hospital for 5 days and 6-hourly blood pressure observations, daily urinary protein quantitation, twice-weekly full blood counts and tests of renal and liver function were performed. All blood pressure measurements were made by sphygmomanometry with the patient at rest on her side using an appropriate size cuff and the 4th Korotkoff sound to define the diastolic blood pressure. Each patient was asked daily about any symptoms; these were noted. The condition of the fetuses was monitored by ultrasonography fortnightly, by non-stress cardiotocography twice weekly and, where indicated, by acoustic stimulation testing.

At the end of phase I the patients' blood pressures were considered to be controlled if the mean 24-hour diastolic blood pressure on day 5 was 90 mmHg or less. Patients whose blood pressures were successfully controlled in phase I were discharged from the hospital for follow-up in the Pregnancy Hypertension Clinic and entered into phase III of the trial.

Phase II

Patients who completed phase I of the trial but in whom satisfactory blood pressure was not achieved (diastolic blood pressure $\geqslant$ 90 mmHg) were entered into phase II of the trial. In this phase all the patients were treated with a combination of alpha-methyldopa 1 g twice daily and indoramin 50 mg twice daily regardless of their initial treatment. The same

TABLE I. DIAGNOSTIC CATEGORY AND PHASE ONE RECRUITMENT

Category	Methyldopa	Indoramin	Placebo	Total
Primigravid non-proteinuric	3	3	2	8
Multigravid non-proteinuric	8	8	8	24
Primigravid proteinuric	3	4	4	11
Multigravid proteinuric	6	5	6	17

maternal and fetal observations were performed as in phase I of the trial and continued for further 5 days. Patients whose blood pressures were satisfactorily controlled (diastolic blood pressure $\leqslant$ 90 mmHg) were entered into phase III of the trial and discharged for follow-up. Patients whose blood pressure were not controlled at the end of phase II were regarded as treatment failures and withdrawn from the trial.

Phase III

Those patients successfully treated in phases I and II were discharged for outpatient follow-up. During this phase the continuing efficacy of the treatment and patient compliance during the remainder of the pregnancy was assessed.

Withdrawals

Patients were withdrawn from the trial in any phase if they developed significant deterioration in the maternal condition (increasing proteinuria and/or decreasing renal function) or any signs of impaired fetal well-being irrespective of the blood pressure level. Non-compliant patients were also withdrawn. These patients were all categorised as 'withdrawals'. Those patients who required additional antihypertensive treatment because of severe hypertension (diastolic blood pressure $\geqslant$ 120 mmHg) or failure to control the blood pressure at the end of phase II or during phase III were categorised as treatment failures.

Statistics

The mean arterial pressures (MAP) were analysed by one-way analysis of variance and numbers of patients controlled in each group by Fisher's exact test.

Results

A total of 60 patients were recruited into the trial and their distribution according to parity and the presence or absence of proteinuria is shown in Table I. The largest group comprised non-proteinuric multiparous patients. Equal numbers of patients were allocated to treatment with alpha-methyldopa, indoramin and placebo within patient groups according to a randomised block design.

Demographic data and baseline renal function are shown in Tables II and III.

TABLE II. DEMOGRAPHIC DATA (MEAN $\pm$ SD)

Category	Gestational age at recruitment (wks)	Maternal age (yrs)
Non-proteinuric primigravida	**31,8 $\pm$ 1,9**	**23 $\pm$ 8**
Proteinuric primigravida	**29,9 $\pm$ 2,3**	**23 $\pm$ 6**
Non-proteinuric multiparous	**31,7 $\pm$ 2,4**	**31 $\pm$ 8**
Proteinuric multiparous	**30,5 $\pm$ 2,3**	**29 $\pm$ 6**

Phase I — non-proteinuric patients (Table IV)

The blood pressure was controlled in a significant proportion of non-proteinuric multiparous patients but there were no significant differences between the proportion of patients controlled by alpha-methyldopa, indoramin or placebo. The fall in MAP in the methyldopa group was, however, significantly greater than in the placebo group. The fall in MAP in the indoramin group was not significantly different from that in the placebo group. In the non-proteinuric primigravid patients the alpha-methyldopa group had the greatest fall in MAP but this was not statistically significantly greater than placebo. None of these patients achieved satisfactory blood pressure control regardless of the treatment administered.

Phase I — proteinuric patients (Table V)

Among the proteinuric multiparous patients neither alpha-methyldopa nor indoramin showed any statistically significant advantage over placebo either in the reduction of average MAP or the numbers of patients controlled. The proteinuric primigravid patients similarly showed no fall in blood pressure.

Phase II (Table VI)

In the second phase of the trial 32 out of the original 60 patients started combined treatment with indoramin and alpha-methyldopa. In this phase the blood pressure was controlled in 5 out of the 14 non-proteinuric patients but only 2 out of the

TABLE III. BASELINE RENAL FUNCTION (MEAN $\pm$ SD)

Category	Serum urea (μmol/l)	Serum creatinine (μmol/l)	Serum urate (μmol/l)	Urinary protein excretion (g/24 h)
Non-proteinuric primigravida	**2,7 $\pm$ 1,1**	**63,1 $\pm$ 16,7**	**0,31 $\pm$ 0,13**	**—**
Proteinuric primigravida	**3,5 $\pm$ 0,7**	**68,4 $\pm$ 11,1**	**0,36 $\pm$ 0,06**	**1,66 $\pm$ 0,59**
Non-proteinuric multiparous	**2,7 $\pm$ 0,7**	**61,7 $\pm$ 9,6**	**0,29 $\pm$ 0,06**	**—**
Proteinuric multiparous	**2,9 $\pm$ 1,0**	**65,3 $\pm$ 15,2**	**0,31 $\pm$ 0,07**	**2,15 $\pm$ 1,75**

TABLE IV. NON-PROTEINURIC PATIENTS, OUTCOME PHASE I

	Methyldopa		Indoramin		Placebo	
	M	P	M	P	M	P
No. recruited	8	3	8	3	8	2
No. controlled	4	0	3	0	2	0
Withdrawal	2	2	1	0	1	0
Failures	2	0	1	0	0	0
Mean change in MAP (mmHg)	−17*	−14,7	−7,8	−2,7	1,1	−2,5

*Indicates statistically significant difference compared with placebo.
M = multigravid; P = primigravid.

TABLE V. PROTEINURIC PATIENTS, OUTCOME PHASE I

	Methyldopa		Indoramin		Placebo	
	M	P	M	P	M	P
No. recruited	3	6	4	5	4	6
No. controlled	0	1	0	0	0	0
Withdrawal	0	1	0	0	0	2
Failures	0	0	0	2	1	3
Mean change in MAP (mmHg)	0	−8,3	−0,5	2,6	3,8	4,8

M = multigravid; P = primigravid.

18 proteinuric patients. Analysis of phases I and II (Table VII) combining all treatments showed that the blood pressure was controlled in a statistically significantly greater percentage of the non-proteinuric group of patients in comparison with the proteinuric group.

Phase III

Only 17 patients were discharged on treatment for follow-up in phase III of the trial and only 7 of these (all non-proteinuric) remained satisfactorily controlled on the trial drugs.

Withdrawals

An analysis of the patients withdrawn showed that there were no significant differences between the methyldopa, indoramin and placebo group in phase I and that the overall indication for withdrawal was almost equally divided between fetal and maternal indications. None of the withdrawals were due to side-effects during treatment.

TABLE VII. OUTCOME PHASE I AND II COMBINED

	Outcome	Non-proteinuric	Proteinuric
Single agent	Entered	32	28
	Controlled	9*	1
	Withdrawn	6	3
	Failure	3	6
Combination methyldopa plus indoramin	Entered	14	18
	Controlled	5	2
	Withdrawn	3	6
	Failure	6	10
Total controlled		14*	3

*Indicates statistical significance.

Discussion

Indoramin is an α_1-postsynaptic adrenergic antagonist that reduces blood pressure through peripheral vasodilatation. Important pharmacological properties of the drug include the selectivity of its action on the α_2-postsynaptic receptors as well as its membrane-stabilising properties, both of which contribute to the absence of tachycardia, which characterises other α-adrenergic receptor blockers.[9]

The drug was initially found to be of benefit in the treatment of non-pregnant patients with hypertension and a co-existing medical problem (such as obstructive airways disease) that would contraindicate the use of a β-blocker.

An uncontrolled study in 21 patients with a contraindication to β-blocker therapy showed a 90% satisfactory response rate when indoramin was combined with diuretic therapy.[10] The use of the drug in the treatment of mild-to-moderate essential hypertension was studied in a double-blind cross-over study comparing the efficacy of indoramin with alpha-methyldopa. This study revealed that both drugs produced satisfactory control of blood pressure and that no differences existed with regard to the incidence of side-effects.[11]

In 1981 the results of 7 long-term clinical trials involving the use of indoramin for the treatment of essential hypertension were analysed and 60% of the patients treated were found to have had an 'excellent' response, 25% a 'good' response and only 15% a 'poor' response.[12]

The acute and chronic cardiovascular effects of indoramin and prazosin have been compared in normal man and the 'first dose' syncopal effect of prazosin was found to be absent with indoramin. This was attributed to the greater venodilating effects of prazosin compared with indoramin.[13] The lack of an ideal antihypertensive agent in the treatment of pregnancy hypertension and the successful use of indoramin in the treatment of hypertension in non-pregnant subjects suggested that a clinical trial of indoramin in hypertension of pregnancy would be of value, particularly in view of its action as an α_1-postsynaptic adrenergic antagonist and a vasodilator.

TABLE VI. OUTCOME OF THERAPY WITH METHYLDOPA AND INDORAMIN, PHASE II

Outcome	Primigravid non-proteinuric	Multiparous non-proteinuric	Primigravid proteinuric	Multiparous proteinuric
Entered	6	8	8	10
Controlled	3	2	1	1
Withdrawn	2	1	1	5
Failure	1	5	6	4

In our trial the patients were grouped on the basis of parity and the presence of proteinuria, since the hypertensive disorders of pregnancy are probably not one entity but a number of different disorders. The trial showed that the use of antihypertensive drugs in the doses specified on the population studied is, for the most part, unsuccessful and that this is particularly so in the case of patients who not only have hypertension but proteinuria as well. The non-proteinuric multiparous patients who responded to treatment were almost certainly latent or chronic essential hypertensive subjects.

Indoramin did not produce a statistically significant reduction in MAP compared with placebo, whereas alpha-methyldopa did so in at least one group of patients. The relative failure of methyldopa in this trial compared with the results of other trials may be due to methodological differences; the Oxford group restricted their study to the treatment of non-proteinuric patients and employed different criteria to establish the antihypertensive efficacy of the drug.[14]

Neither indoramin nor methyldopa was associated with any side-effects in the dosages used. In particular, none of the patients on alpha-methyldopa complained of drowsiness in spite of this being a well-reported side-effect of this drug. Analysis of the 'withdrawals' showed that all were due to deterioration in the condition of the mother or the fetus and progression of the underlying disease.

Indoramin and alpha-methyldopa would appear to have a limited role to play in the management of patients with hypertension in pregnancy. The combination of methyldopa and indoramin, however, may increase the number of patients who attain satisfactory blood pressure control, particularly where single-agent therapy has failed. In the dosages used, both indoramin and methyldopa only produced satisfactory control in about 50% of patients and this was almost entirely confined to non-proteinuric patients and even then the duration of effectiveness was limited. The use of indoramin and α-adrenergic antagonists as single agents in the treatment of hypertension in pregnancy appears to be limited.

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REFERENCES

1. Lamming GD, Broughton Pipkin F, Syndonds EM. Comparison of the alpha- and beta-blocking drug, labetolol, and methyldopa in the treatment of moderate and severe pregnancy-induced hypertension. *Clin Exp Hypertens* [*A*] 1980; **2:** 865-895.
2. Leather HM, Humphreys DM, Baker P, Chadd MA. A controlled trial of hypotensive agents in hypertension in pregnancy. *Lancet* 1968; **2:** 488-490.
3. Redman CWG, Beilin LJ, Bonnar J, Ounsted MK. Fetal outcome in trial of antihypertensive treatment in pregnancy. *Lancet* 1976; **2:** 753-756.
4. Rubin PC, Butters L, Clark DM *et al.* Placebo-controlled trial of atenolol in treatment of pregnancy-associated hypertension. *Lancet* 1983; **1:** 431-434.
5. Fidler J, Smith V, Fayers P, De Swiet M. Randomised controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. *Br Med J* 1983; **286:** 1927-1930.
6. Gallery EDM, Ross MR, Gyory AZ. Antihypertensive treatment in pregnancy: analysis of different responses to oxprenolol and methyldopa. *Br Med J* 1979; **291:** 563-566.
7. Coltart J. Clinical pharmacological studies of indoramin in man. *Br J Clin Pharmacol* 1981; **12:** 49S-60S.
8. Coleman AJ. Evidence for increase in peripheral blood flow by indoramin in man. *Br J Clin Pharmacol* 1981; **12:** 49S-60S.
9. Alps BJ, Hill M, Fidler K, Johnson ES, Wilson AB. Reversal of experimental arrythmias by indoramin (WY 21901). *Br J Clin Pharmacol* 1971; **23:** 678-686.
10. Zacharias FJ. Utility of indoramin in patients unable to tolerate β-blockers. *Br J Clin Pharmacol* 1981; **12:** 105S-109S.
11. Rosendorff C. Indoramin and hypertension: clinical studies. *Br J Clin Pharmacol* 1981; **12:** 89S-93S.
12. Johnson ES. Indoramin in essential hypertension: a survey of the patient records from long-term clinical trials. *Br J Clin Pharmacol* 1981; **12:** 131S-137S.
13. Nicholls DP, Harron DWG, Shanks RG. Acute and chronic cardiovascular effects of indoramin and prazosin in normal man. *Br J Clin Pharmacol* 1981; **12:** 61S-66S.
14. Redman CWG, Beilin LJ, Bonnar J. Treatment of hypertension in pregnancy with methyldopa: blood pressure control and side effects. *Br J Obstet Gynaecol* 1977; **84:** 419-426.