PAPERS AND ORIGINALS

Randomised comparison of methyldopa and oxprenolol for treatment of hypertension in pregnancy

E D M GALLERY, D M SAUNDERS, S N HUNYOR, A Z GYÖRY

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Summary and conclusions

Fifty-three pregnant women with moderately severe hypertension were randomly allocated to treatment with methyldopa or oxprenolol. There were no significant differences between the groups in age, height, weight, parity, or stage of gestation at the start of treatment. The outcome of pregnancy was better in the group treated with oxprenolol, with greater maternal plasma volume expansion and placental and fetal growth. No intrauterine deaths occurred in either group, and antepartum fetal distress, detected by oxytocin challenge testing, was evident in only one patient, who received methyldopa. This infant, and one other in the methyldopa group, died in the neonatal period. No neonatal deaths occurred in the oxprenolol-treated group. Even in this small number of patients these results were considerably better than those in untreated women with hypertension of similar severity. Apgar scores in both groups were equivalent at birth, while blood sugar concentrations were higher in the oxprenolol group.

Oxprenolol appears to be safe and effective in controlling hypertension during pregnancy. There was no evidence of harmful effects on the fetus, and oxprenolol may offer a selective advantage over methyldopa for fetal growth and wellbeing in utero.

Departments of Medicine, Cardiology, and Obstetrics and Gynaecology, Royal North Shore Hospital, St Leonards, NSW, Australia

E D M GALLERY, MB, FRACP, research fellow, National Heart Foundation of Australia

D M SAUNDERS, MD, MRCOG, associate professor of obstetrics and gynaecology, Sydney University

S N HUNYOR, FRACP, FACC, research specialist in cardiology

A Z GYÖRY, MD, FRACP, associate professor of medicine, Sydney University

Introduction

Hypertension during pregnancy causes an appreciable increase in maternal and perinatal morbidity and in fetal and neonatal mortality.[1 2] In untreated severely hypertensive women intrauterine growth retardation is common[3] and the risk of fetal loss is high at all stages of gestation.[4 5] Antihypertensive treatment reduces the incidence of sudden rises in blood pressure and improves the perinatal outcome.[6] The antihypertensive agent most often studied in pregnancy, methyldopa, though having no harmful effects on the fetus,[6-8] has not been shown actively to improve fetal growth or wellbeing except for a possible reduction in the incidence of midtrimester abortion,[8] a risk that is increased in women with severe hypertension.[5]

To examine the effects of antihypertensive treatment more closely and to evaluate alternative forms of treatment we conducted a randomised comparison of methyldopa and a non-selective beta-adrenoceptor-blocking drug, oxprenolol.

Methods

All patients included in the study were attending Royal North Shore Hospital for antenatal care. Initially 56 patients started treatment, but three were excluded from analysis, of whom two were expecting twins and one triplets. The criterion for entry into either treatment group was a sitting diastolic blood pressure (BP) (phase IV, Korotkoff sounds) at or above either 95 mm Hg on two occasions at least 24 hours apart or 100 mm Hg on two occasions at least eight hours apart, at any stage of pregnancy. On each occasion the mean of two readings taken one minute apart, after 10 minutes' sitting quietly, was recorded. All BP measurements were made with a Hawksley random zero sphygmomanometer. Patients were allocated randomly to treatment with either methyldopa or oxprenolol. We also included in the study 10 patients with hypertension who had been receiving treatment before pregnancy. Their treatment was altered at presentation to either drug under study in the same randomised fashion. All outpatients were seen fortnightly till 28 weeks of amenorrhoea and weekly thereafter, alternately by their own obstetricians and at a special medical clinic. All inpatients were seen and assessed daily. Whenever possible gestational age was confirmed before 20 weeks by ultrasound examination.

The dosage of either drug was altered as clinically indicated to maintain a sitting diastolic BP at or below 80 mm Hg. When necessary

hydrallazine was added to either treatment regimen for improved BP control.

Serum creatinine and urate concentrations and haematological and coagulation state were monitored regularly. Plasma volume was measured with Evans blue, as described elsewhere,[9] at 33-36 weeks' amenorrhoea in 19 patients in each group, and the results were expressed as a function of maternal height. External fetal cardiotocography was performed weekly by a neonatologist from 32 weeks of amenorrhoea till delivery, with oxytocin challenge testing performed when indicated by abnormal unstressed fetal heart rate patterns.

As the plasma volume was found to be log-normally distributed, values given for grouped results are geometric means ± SE, whereas other grouped data are represented by the arithmetic mean ± SE. The statistical significance of differences between groups was tested by Student's t test. The χ^2 test was used to compare modes of delivery in the two treatment groups, and analysis of variance to remove the effect of gestational age on birth weight. Multiple regression analysis was used to study the interrelation between maternal, fetal, and placental weights. When appropriate we compared the results with normal results in our own obstetric population.

Results

There was no significant difference between the two groups in age, parity, stage of pregnancy, or severity of hypertension before treatment was begun (table I). The stage of pregnancy and severity of hypertension were calculated excluding the 10 women who were transferred from some other form of treatment in early pregnancy (all before 20 weeks of amenorrhoea), but these patients were included in the analyses of all results obtained after the start of either oxprenolol or methyldopa. The stage of pregnancy at delivery was not significantly different in the two groups, nor were the modes of delivery, although there was a trend towards lower segment caesarean section in the methyldopa group and towards spontaneous labour in the oxprenolol group. No patient in either group went into spontaneous labour before the 38th week of gestation.

Serum creatinine and urate concentrations (table II) were measured monthly in all patients receiving treatment until 32 weeks of amenorrhoea and weekly thereafter. The only significant difference from our normal obstetric population occurred in serum urate concentrations in both groups between 29 and 32 weeks of amenorrhoea. This was due to a rapid and severe exacerbation of hypertension with the development of proteinuria in two patients in each group, associated with severe hyperuricaemia and necessitating urgent premature delivery at 31 weeks' gestation by lower-segment caesarean section in three cases. In the fourth patient, who underwent caesarean section at 33 weeks of amenorrhoea, BP control with oxprenolol and hydrallazine was extremely poor, her diastolic BP never falling below 95 mm Hg. She became hypotensive intraoperatively, requiring large volumes of intravenous fluids. Her postpartum course was complicated by the occurrence of acute tubular necrosis, from which she recovered fully. Her baby suffered no ill effects.

The haemoglobin concentration, packed cell volume, and platelet count were measured at monthly intervals during pregnancy and remained normal in both groups.

BP control was adequate and equivalent in the two groups, as seen in fig 1, which shows for comparison the mean systolic and diastolic pressures (and two SDs above the mean of each) in our normal obstetric population.[10] Mean dosages of each drug are also given.

TABLE I—*Clinical data before start of treatment and at delivery for mothers treated with oxprenolol or methyldopa. Figures are means ± SE of mean*

	Oxprenolol group	Methyldopa group
Ratio of primigravidae:multigravidae	17:9	21:6
Age (years)	28·5 ± 0·74	27·7 ± 0·95
Height (cm)	165 ± 1·3	162·6 ± 1·3
Weight before pregnancy (kg)	58·9 ± 1·7	57·9 ± 2·3
Sitting BP at start of treatment (mm Hg)	147 ± 2·74/102 ± 2·48	151 ± 2·36/102 ± 1·93
Weeks of amenorrhoea at start of treatment	31 ± 1·8	32 ± 0·8
Weeks of amenorrhoea at delivery	38 ± 0·4	37·5 ± 0·6
Mode of delivery:		
Spontaneous vaginal	6	3
Induction, vaginal	13	13
Lower-segment caesarean section	7	11

BP = Blood pressure.
There were no significant differences between the groups.

TABLE II—*Sequential values of serum creatinine and urate concentrations in patients treated with oxprenolol or methyldopa. Results expressed as means ± SE of mean*

Weeks of amenorrhoea	Serum creatinine (mmol/l)		Serum urate (mmol/l)	
	Oxprenolol group	Methyldopa group	Oxprenolol group	Methyldopa group
13-16	0·08 ± 0·014	0·06 ± 0·003	0·29 ± 0·046	0·24 ± 0·022
17-20	0·06 ± 0·006	0·06 ± 0·005	0·22 ± 0·019	0·22 ± 0·016
21-24	0·07 ± 0·009	0·05 ± 0·006	0·26 ± 0·028	0·24 ± 0·019
25-28	0·07 ± 0·012	0·07 ± 0·005	0·27 ± 0·067	0·32 ± 0·028
29-32	0·08 ± 0·012	0·08 ± 0·007	0·36 ± 0·047	0·40 ± 0·036
33-34	0·08 ± 0·008	0·04 ± 0·005	0·33 ± 0·039	0·32 ± 0·032
34-35	0·08 ± 0·008	0·07 ± 0·004	0·31 ± 0·047	0·32 ± 0·025
35-36	0·06 ± 0·004	0·07 ± 0·006	0·32 ± 0·028	0·33 ± 0·019
36-37	0·07 ± 0·003	0·07 ± 0·004	0·38 ± 0·021	0·32 ± 0·021
37-38	0·08 ± 0·010	0·06 ± 0·005	0·37 ± 0·021	0·32 ± 0·018
38-39	0·07 ± 0·015	0·07 ± 0·005	0·36 ± 0·046	0·31 ± 0·026

Conversion: SI to traditional units—Serum creatinine: 1 mmol/l ≈ 11·3 mg/100 ml. Serum urate: 1 mmol/l ≈ 16·8 mg/100 ml.

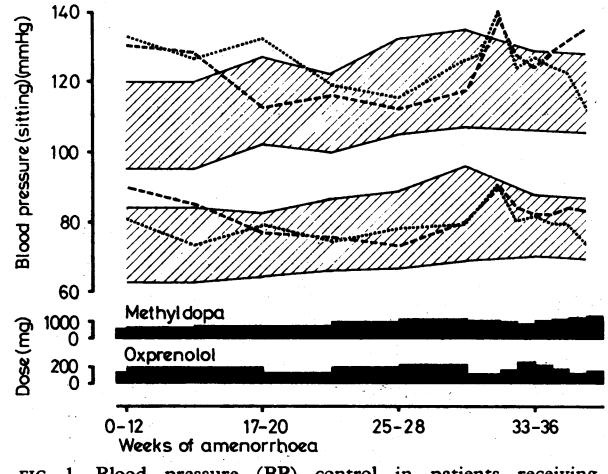

FIG 1—Blood pressure (BP) control in patients receiving oxprenolol (- - -) and methyldopa (. . .) during pregnancy. For comparison hatched area indicates normal systolic and diastolic BPs in our obstetric population (mean and 2 SDs above the mean). Dosages of both drugs are also shown.

TABLE III—*Clinical data on babies born to women treated with oxprenolol or methyldopa. Results are expressed as means ± SE of mean*

	Oxprenolol	Methyldopa	P
Sex (M:F)	15:11	16:11	
Birth weight:			
Weight (g)	3051 ± 129·8	2654 ± 158·1	<0·05
% of normal for gestational age	95 ± 3·1	83 ± 3·6	<0·01
Placental weight:			
Weight (g)	534 ± 23·1	479 ± 27·0	NS
% of normal for gestational age	85 ± 3·4	76 ± 3·6	<0·05
Apgar score:			
At 1 minute	7·8 ± 0·36	7·6 ± 0·33	NS
At 5 minutes	9·4 ± 0·16	9·2 ± 0·23	NS
Blood glucose concentration (mmol/l)	3·8 ± 0·27	2·8 ± 0·36	<0·05
No of intrauterine deaths	0	0	
No of neonatal deaths	0	2	

NS = Not significant.
Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

It was necessary to add hydrallazine for better control in 11 patients receiving oxprenolol and seven receiving methyldopa, the mean durations of treatment with hydrallazine before delivery being 14 and five weeks respectively; these were not significantly different from each other due to wide variation.

Table III gives information on the babies born in the two groups. Babies in the oxprenolol group were on average 400 g heavier than those in the methyldopa group, the difference being significant. They were also of normal weight, while those in the methyldopa group were significantly growth-retarded ($P < 0·001$) compared with our normal population at the same age of gestation. Normal values were obtained from serial ultrasound and delivery data.[11] Figures for normal placental weight at different stages of gestation were taken from the report by

Thomson *et al*,[12] and placental weight in the methyldopa group was significantly ($P < 0.01$) lower than normal for the stage of gestation at delivery. The mean Apgar score of babies in both groups was normal at one and five minutes after delivery. Blood sugar concentrations (Dextrostix) were normal in babies in the oxprenolol group and significantly ($P < 0.05$) higher than those in the methyldopa group. None of the babies in the oxprenolol group was clinically hypoglycaemic, while two in the methyldopa group were and required intravenous dextrose. No intrauterine deaths occurred, and the only two neonatal deaths occurred in the methyldopa group, both related to extreme prematurity.

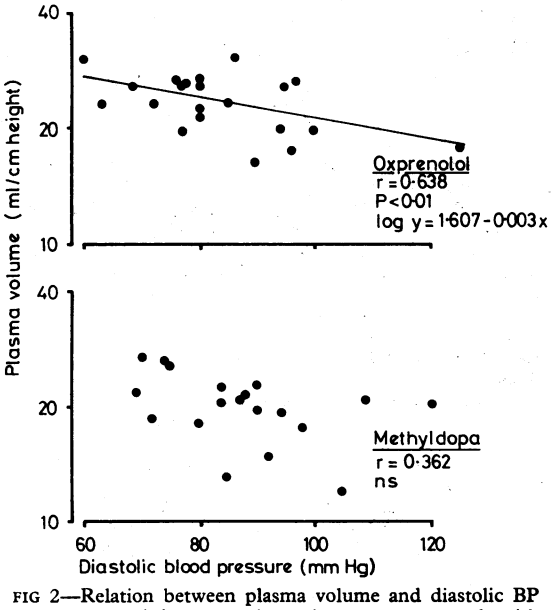

FIG 2—Relation between plasma volume and diastolic BP at 33-36 weeks' amenorrhoea in women treated with oxprenolol or methyldopa.
NS = Not significant.

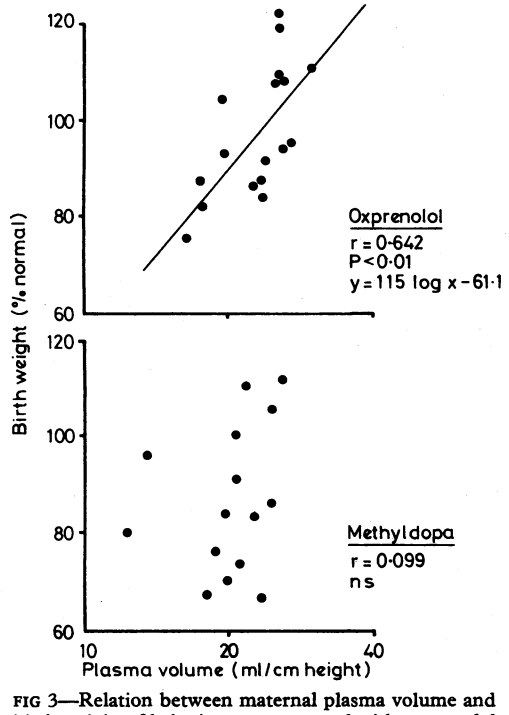

FIG 3—Relation between maternal plasma volume and birth weight of baby in women treated with oxprenolol or methyldopa.
NS = Not significant.

Figure 2 shows the relation, in 19 patients in each group, between the BP and log plasma volume at 33-36 weeks of amenorrhoea. There was a weak relation that failed to reach significance in the patients receiving methyldopa, while BP control in the oxprenolol group was associated closely with plasma volume expansion. The relation between plasma volume expansion at 33-36 weeks of amenorrhoea and the birth weight of babies was weak in patients receiving methyldopa and failed to reach significance (fig 3). The greater degrees of volume expansion achieved in the oxprenolol group were associated with better fetal growth and hence improved birth weight, a selective advantage for the babies of these women.

Discussion

Both forms of treatment satisfactorily controlled maternal hypertension (fig 1). The individual drug dosage was determined by the sitting diastolic BP, the aim being to maintain it at or below 80 mm Hg, 2 SD above the mean in our normal obstetric population for most of the pregnancy. It has been suggested that treatment with beta-adrenergic-blocking drugs might subject women to an increased risk of premature labour,[13] but in none of our patients was this observed. Side effects of treatment were in fact few in both groups, the major one being a subjective sensation of lethargy and drowsiness in three women treated with methyldopa.

Significant differences occurred between the treatments in respect of the fetus. Both placental and birth weights were significantly greater for the stage of gestation in the oxprenolol group (table I). The differences were not attributable to an effect of maternal body weight, as the normal interrelation of these variables, maintained in the oxprenolol group, was disturbed in the methyldopa group, where the dependence on maternal weight of the other two factors was lost. If maternal body weight is x, placental weight y, and birth weight z, their partial correlation coefficients are as follows. (1) Oxprenolol: $r_{xy \cdot z} = 0.179$ (not significant (NS)); $r_{xz \cdot y} = 0.405$ ($P < 0.05$); $r_{yz \cdot x} = 0.492$ ($P < 0.05$). (2) Methyldopa: $r_{xy \cdot z} = 0.091$ (NS); $r_{xz \cdot y} = 0.181$ (NS); $r_{yz \cdot x} = 0.650$ ($P < 0.01$). Hydrallazine treatment was not responsible for the improved fetal outcome, as in both groups the women needing hydrallazine had significantly smaller babies than those well controlled with a single agent (women receiving oxprenolol and hydrallazine: birth weight 2918 ± 170 g, 37 ± 0.5 weeks' amenorrhoea; methyldopa and hydrallazine: birth weight 2474 ± 178 g, 37 ± 0.6 weeks' amenorrhoea).

A highly significant inverse relation exists in untreated hypertensive women between plasma volume and BP[9] whether they are pregnant[9] or not.[14] The desirability of plasma volume expansion in normotensive pregnant women has been recognised for some time, being associated with improved fetal growth,[15] while plasma volume contraction is associated with fetal growth retardation in both hypertensive women[16] and normotensive women with placental insufficiency.[17] Correction of hypertension with oxprenolol reversed this volume contraction, probably permitting improved placental blood flow, resulting in larger placentas and improved intrauterine growth. The same degree of BP control in the methyldopa group (fig 1) did not achieve reversal of the volume contraction. The mean plasma volume in this group at 33-36 weeks' amenorrhoea (19.9 ± 1.05 ml/cm height) was significantly lower than normal for this stage of gestation (23.1 ± 1.02 ml/cm height, $P < 0.001$)[9] and than the volume in the oxprenolol group (24.0 ± 1.04 ml/cm height), which in turn was not significantly different from normal.

Anecdotal reports have suggested that treating pregnant women with propranolol is associated with increased perinatal morbidity and mortality related to placental insufficiency, neonatal hypoglycaemia, respiratory depression, or severe bradycardia.[18-21] In none of the reports cited do these claims bear close scrutiny, and there is more than one other potential cause for the complications listed.

In a retrospective survey of women treated with various antihypertensive drugs in pregnancy, Lieberman *et al*[22] suggested

that propranolol caused an increase in the intrauterine death rate in their population. Unfortunately, in their report little information is given about potential risk factors in their patients and there is no discussion of the adequacy of control of hypertension and inadequate discussion of the effect of concomitant diuretic treatment and the particularly high incidence of underlying severe chronic renal disease in patients treated with propranolol—all of these are factors that must be considered in any attempt to examine possible effects of treatment on the fetus in utero.

While beta-adrenoceptor-blocking drugs are similar in their antihypertensive effect, their other pharmacological properties are often greatly dissimilar. In animals oxprenolol causes less bradycardia than propranolol[23] and a fall in peripheral vascular resistance where propranolol causes an increase, and has appreciably less negative (and sometimes positive) inotropic activity than propranolol.[23–25] Little is known about the pharmacokinetics of any of the beta-adrenoceptor-blocking agents in human pregnancy. Most experimental data are from the chronically instrumented pregnant ewe given intravenous propranolol.[26 27] The relevance of results with this preparation to pregnant women is most uncertain. Similarly, the results of short-term human studies using either intrauterine injection of propranolol[28] or the simultaneous intravenous administration of propranolol and various vasoactive substances[29–31] are difficult to apply to the clinical treatment of hypertension. The effects of oxprenolol observed in this study may well not be achieved with other non-selective beta-adrenoceptor-blocking drugs, and these results cannot therefore be generally applied to the entire class until the appropriate comparative studies are performed.

In this randomly selected population of pregnant women with moderately severe hypertension there was no suggestion of adverse fetal effects resulting from treatment with oxprenolol; on the contrary, its use was associated with an improved fetal outcome. As adverse effects result from a sitting diastolic BP above 85 mm Hg,[9] a persistently raised diastolic BP to 90 mm Hg, not controlled by bed rest and at any stage of pregnancy, constitutes an indication for antihypertensive treatment if delivery is not imminent. Oxprenolol is an effective and perhaps selectively beneficial form of treatment for use in these circumstances.

One of us (EDMG) was a postgraduate medical research scholar of the National Heart Foundation of Australia at the time of this study.

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ONE HUNDRED YEARS AGO During the last few weeks, Dr Garson, the Anatomical Assistant at the Royal College of Surgeons, has been engaged making a series of frozen sections of the body, and has succeeded in getting some very beautiful longitudinal and transverse sections. This method has been for several years practised on the Continent, first by Pirogoff in Russia, and then by Braune in Leipzig, whose pupil Dr Garson was, and from whom he learned the method; and by several others. Dr Garson has, we believe, been the first to introduce the method into this country on any large scale, although it has been done on a small scale before. We learn that Dr Garson first injects both the arteries and veins with a composition coloured red for the arteries and blue for the veins. The body is then put into a watertight tank made of galvanised sheet-iron. The whole is then surrounded with a mixture of salt and ice, and allowed to remain for three or four days, according to the degree of cold that has been obtained, the ice and salt being renewed and stirred up when required. The temperature of the mixture must be carefully attended to, as it is only from that that it can be known when the body is thoroughly frozen. When ready, the body should be like a log of hard wood, and may be cut with a fine-toothed saw in any direction and through all its structures. The sections must then be washed with ice-cold water, so as to remove the sawdust, and immediately placed in spirit, when they are allowed to thaw and afterwards reharden. When thoroughly hardened in spirit, they may be taken out and dressed up with a section-knife, and are then ready for mounting permanently. Several small details require to be attended to in making those frozen sections, otherwise failures are apt to happen. The sections we have seen at the College of Surgeons exhibit in a remarkable manner the relations of the various organs and structures in the body. The longitudinal mesial section and those of the left side of the body are naturally the most interesting from their showing the relations of the majority of the organs. We understand that the sections are for the museum, and will be a valuable addition to the magnificent collection of normal anatomy which it contains. The cost of making these sections is considerable; however, as they are very valuable, we hope Dr Garson will complete the series of them by making a set of transverse ones. In the meantime, we may congratulate Dr Garson on his having succeeded in freezing the bodies so thoroughly and obtaining such fine sections. We must also congratulate Professor Braune on sending us such an apt pupil, and the Council of the College of Surgeons and the conservator of the museum in being able to engage his valuable services. To meet the convenience of many of the fellows and members who desire to see these sections, Dr Garson proposes to show them, and explain the process, in the Museum of the College of Surgeons, at 2 pm on each Thursday during February. (*British Medical Journal*, 1879.)