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Antihypertensive treatment in pregnancy: analysis of different responses to oxprenolol and methyldopa

E D M GALLERY, M R ROSS, A Z GYORY

Abstract

One hundred and eighty three hypertensive pregnant women were randomly assigned to antihypertensive treatment with oxprenolol (96 women) or methyldopa (87 women). Control of hypertension was equivalent in both treatment groups, and in 64 (35%) cases hydralazine had to be added to the treatment to achieve the therapeutic goal (diastolic blood pressure below 85 mm Hg). Five perinatal deaths occurred, one in the oxprenolol group and four in the methyldopa group. Detailed analysis confirmed a previous report of greater fetal growth in the group treated with oxprenolol; this trend was present regardless of severity of hypertension and parity. With increasing duration of treatment the differences between the two groups diminished, and there was no difference after 10 weeks of treatment, a finding that may explain some of the reported discrepancies among therapeutic studies.

As hypertension in pregnancy may pursue an accelerated course, necessitating urgent delivery, and there is no satisfactory method of predicting the duration of treatment in individual patients fetal benefit is most likely to be achieved by treatment with oxprenolol, provided that there is no maternal contraindication to treatment with β blockers.

Introduction

Hypertension in pregnancy, whatever its aetiology, remains the most common medical cause of both maternal and perinatal morbidity and mortality.[1 2] It has been clearly shown that control of hypertension reduces these complications,[2-4] although the choice of antihypertensive agent is controversial.[5-7]

We previously reported preliminary results of the first randomised comparison of a β adrenoceptor blocking agent and the centrally acting agent methyldopa for the treatment of hypertension in pregnancy.[8] This report deals with the completed study, in which 183 pregnant women participated.

Patients and methods

All patients included in the study were attending this hospital for antenatal care. One hundred and eighty three women with singleton pregnancies complicated by hypertension were allocated by a series of random numbers to treatment with either oxprenolol or methyldopa. Neither the patient nor the doctor was blinded regarding treatment. The criterion for entry into the study was a sitting diastolic blood pressure (phase IV, Korotkoff sounds) of 90 mm Hg or above on two occasions at least 24 hours apart, 95 mm Hg or above on two occasions 12 hours apart, or 100 mm Hg or above on two occasions eight hours apart. On each occasion the mean of two readings taken one minute apart after the patient had been sitting quietly for 10 minutes was recorded. All patients were inpatients at the time of starting treatment and remained so until adequate control of blood pressure was achieved. After this patients were treated as outpatients unless there was a specific indication to remain in hospital. Outpatients were seen fortnightly until 28 weeks of amenorrhoea and weekly thereafter, alternately by their own obstetricians and at a special medical obstetrical clinic. Inpatients were seen and assessed daily.

Oxprenolol was started at a dose of 40 mg twice daily and methyldopa at 250 mg twice daily, subsequent doses of both drugs being altered as clinically indicated to maintain a sitting diastolic blood pressure of 80 mm Hg or below. If control of hypertension was not achieved at a dose of oxprenolol 240 mg daily or methyldopa 2 g daily hydralazine was added to the treatment regimen at a starting dose of 12·5 mg twice daily. Maximum daily drug doses were, respectively, oxprenolol 640 mg, methyldopa 3 g, and hydralazine 300 mg. In 12 patients all three antihypertensive agents were necessary to achieve control of hypertension.

Seventeen patients included in the study had been receiving treatment before pregnancy. Their treatment was altered at presentation to either drug under study in the same randomised fashion (nine to oxprenolol, eight to methyldopa). Their values were excluded from the calculation of the stage of pregnancy and severity of hypertension at the start of treatment, but they were included in the analysis of all results obtained after the start of either drug.

Departments of Renal Medicine and Medicine, Sydney University, Royal North Shore Hospital, St Leonards, NSW 2065, Australia

E D M GALLERY, MD, FRACP, research fellow, National Health and Medical Research Council of Australia

M R ROSS, SRN, nursing sister

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

Correspondence to: Dr Gallery.

Serum creatinine and urate concentrations, liver function, and haematological and coagulation state were monitored regularly, and unstressed fetal cardiotocography was performed weekly from 32 weeks of amenorrhoea until delivery, and more regularly if clinically indicated. Delivery was effected for either fetal or maternal indications. Although hyperuricaemia was not a specific indication for delivery, a rate of rise of concentrations in excess of 0·01 mmol/l/week (0·17 mg/100 ml/week) was considered to be abnormal and resulted in closer monitoring of individual patients. Maternal indications for early delivery were: a rise of 50% or more in serum creatinine concentration; the development of coagulopathy; abnormal liver function; or a rapid increase in the clinical severity of disease as assessed by blood pressure, vasospasm, hyperreflexia, hepatic tenderness, and nausea. Fetal indications were: cessation of intrauterine growth shown by ultrasonography and an unreactive cardiotocograph or positive result on challenge testing with oxytocin, or both.

If none of these indications was present patients were delivered electively some time between 37 and 41 weeks of amenorrhoea. All patients were followed up for at least three months post partum for assessment of the need for longer term treatment or further investigation.

STATISTICAL METHODS

Differences between group means were tested by unpaired Student's t test. Comparison of the incidences of complications was by χ^2 analysis, while interrelations of the severity of hypertension, duration of treatment, and fetal growth were assessed by multiple regression analysis.[9]

A combined standard error (SE) for the two treatment groups was calculated by using the sums of squares from the regression obtained by multiple regression analysis for each treatment group, according to the formula:

$$SE = \sqrt{\frac{SS_1 + SS_2}{(N_1 - 3) + (N_2 - 3)} \times \frac{N_1 + N_2}{N_1 \times N_2}}$$

where SS_1 = sums of squares for the group treated with oxprenolol (O), N_1 = total number of patients in the group treated with oxprenolol, SS_2 = sums of square for the group treated with methyldopa (M), and N_2 = total number of patients in the group treated with methyldopa. Significance was then tested for mean weights of treatment groups at different durations of treatment (with diastolic blood pressure before treatment fixed at intervals from 85 to 100 mm Hg) by the formula:

$$t = \frac{\text{mean O} - \text{mean M}}{\text{SE of difference (as calculated above)}}$$

Results

The two groups were comparable in age, height, weight, parity, severity of hypertension, and stage of pregnancy at which treatment was started (table I). All patients completed the study. The time from the start of treatment to delivery varied from two days to 34 weeks (mean eight weeks).

TABLE I—*Mean (SEM) clinical data for all women treated with oxprenolol and methyldopa and for primigravidas alone*

	Oxprenolol group		Methyldopa group	
	Total	Primigravidas	Total	Primigravidas
No in group	96	49 (51%)	87	51 (59%)
Age (years)	28·1 (0·4)	27·2 (0·7)	28·5 (0·5)	28·3 (0·7)
Height (cm)	164 (0·6)	164 (0·8)	164 (0·6)	164 (0·8)
Weight before pregnancy (kg)	60·9 (1·1)	60·5 (1·2)	61·7 (1·3)	61·1 (1·7)
Weeks' gestation at start of treatment*	29 (1·2)	30 (1·7)	30 (1·1)	31 (1·3)
Blood pressure (sitting, before treatment) (mm Hg)*	141/94 (1·5/1·0)	142/95 (2·3/1·5)	142/92 (1·8/1·4)	145/93 (2·2/1·7)

*Calculations exclude nine women given oxprenolol and eight given methyldopa transferred from other treatments, all before 20 weeks' amenorrhoea.

TABLE II—*Therapeutic regimens needed to achieve control of hypertension. Figures are numbers (%) of patients*

	Oxprenolol group		Methyldopa group	
Regimen	Total (n = 96)	Primigravidas (n = 49)	Total (n = 87)	Primigravidas (n = 51)
One drug (oxprenolol or methyldopa)	50 (52)	23 (47)	57 (65)	30 (59)
Two drugs (oxprenolol or methyldopa plus hydralazine)	38 (40)	23 (47)	26 (30)	19 (37)
Three drugs (oxprenolol plus methyldopa plus hydralazine)	8 (8)	3 (6)	4 (5)	2 (4)

TABLE III—*Mode of and indication for delivery in both groups. Figures are numbers (%) of patients*

	Oxprenolol group		Methyldopa group	
	Total (n = 96)	Primigravidas (n = 49)	Total (n = 87)	Primigravidas (n = 51)
Mean (SEM) weeks' gestation at delivery	38·1 (0·2)	38·1 (0·3)	38·0 (0·3)	37·7 (0·4)
Mode of delivery:				
Vaginal (spontaneous labour)	18 (19)	10 (20)	17 (20)	9 (18)
Vaginal (induction)	40 (42)	17 (35)	33 (38)	18 (35)
Lower segment caesarean section	38 (39)	22 (45)	37 (42)	24 (47)
Indication for delivery:				
Maternal	10 (11)	6 (12)	10 (12)	8 (16)
Fetal	5 (5)	2 (4)	9 (10)	6 (12)
Elective or spontaneous	81 (84)	41 (84)	68 (78)	37 (72)

Control of hypertension was adequate and equivalent in both groups. To achieve this hydralazine had to be added to the therapeutic regimen in 64 (35%) patients and the third agent had to be added (that is, methyldopa to the combination of oxprenolol and hydralazine, or oxprenolol to the combination of methyldopa and hydralazine) in 12 (7%) patients, with minor differences between the groups not achieving significance (table II).

There was no significant difference between the groups in the duration of pregnancy at the time of delivery, and no patient in either group went into spontaneous labour before the 28th week of gestation. Table III shows the indications for delivery: acceleration of maternal disease was the indication in 10 (11%) of the patients treated with oxprenolol and 10 (12%) of those treated with methyldopa.

Tables IV and V summarise the perinatal outcome. Mean birth weights in both treatment groups were within the normal range for the total population at this hospital, though they were somewhat higher in the women treated with oxprenolol than in those treated with methyldopa ($p < 0·05$).

Overall, babies born to primigravidas were smaller than those born to multiparous women, and boys were slightly heavier than girls. Babies of women who required only one antihypertensive agent for control of blood pressure were bigger than those of women with more severe hypertension, and there was no significant difference in birth weights between the oxprenolol and methyldopa groups in these mildly hypertensive women. Apgar scores at birth and at five minutes were satisfactory in most babies in both groups, and hypoglycaemia was not a major concern.

Overall, 34 (19%) babies required admission to the intensive care unit (15 (16%) of those treated with oxprenolol and 19 (22%) of those treated with methyldopa; this difference was not significant). The most common reasons for admission to the unit were prematurity (six and five babies in the oxprenolol and methyldopa groups, respectively) and asphyxia (one and four babies, respectively). One intrauterine death occurred in the oxprenolol group (at 32 weeks' gestation), and four neonatal deaths occurred in the methyldopa group (three within a week of delivery and the fourth from the sudden infant death syndrome at 7 weeks of age, shortly after discharge from hospital). All of these babies had been born at less than 34 weeks' gestation and had suffered from severe intrauterine growth retardation with birth weights below 1500 g.

TABLE IV—*Mean (SEM) clinical data for babies born in both treatment groups*

	Oxprenolol group		Methyldopa group	
	Total	Primigravidas	Total	Primigravidas
Sex (M:F)	50:46	30:19	40:47	19:32
Birth weight (g)	3122 (60·5)	3044 (77)	2981 (81·7)	2846 (112)
% of normal birth weight for gestational age	97 (1·4)	94·4 (1·9)	92 (1·9)*	88·6 (2·6)*
Apgar score:				
At 1 minute	7·5 (0·2)	7·9 (0·2)	7·5 (0·2)	7·4 (0·3)
At 5 minutes	9·0 (0·1)	9·2 (0·1)	9·2 (0·1)	9·0 (0·2)
Blood glucose (mmol/l)	3·4 (0·2)	3·4 (0·2)	3·5 (0·2)	3·6 (0·4)
No of intrauterine deaths	1	1		
No of neonatal deaths			4	4
No (%) admitted to neonatal intensive care unit	15 (16)	9 (18)	19 (22)	11 (22)
No of days in neonatal intensive care unit (range)	13 (2-40)	13 (1-45)	13 (2-40)†	13 (1-45)†

*$p < 0·05$.
†Excluding three babies who died within seven days of delivery.
Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

TABLE V—*Mean (SEM) birth weights of babies born to primigravidas*

	Oxprenolol group		Methyldopa group	
	Male	Female	Male	Female
	Birth weight (g)			
All treatment groups	3114 (104)	2933 (113)	3096 (170)	2697 (143)
One drug only	3459 (177)	3036 (116)	3460 (91)	2943 (128)
Two drugs	2969 (117)	2619 (277)	2691 (297)	2381 (338)
	Birth weight as % of normal for gestational age			
All treatment groups	96 (2·5)	92 (2·7)	95 (4·1)	85 (3·2)
One drug only	102 (5·9)	91 (3·5)	105 (3·3)	90 (3·1)
Two drugs	93 (2·2)	93 (4·3)	85 (6·6)	78 (7·3)

Discussion

The first and most important conclusion to be drawn from this and from other recent large scale studies of antihypertensive treatment in pregnancy[10–12] is that results of treatment are superior to the previously described natural clinical course of this common complication of pregnancy. The second clear point is the one that we made tentatively in our original report[8]—namely, that the administration of the β adrenoceptor blocking agent oxprenolol has no adverse effects on fetal outcome in these high risk pregnancies. This finding has been confirmed by others since our initial report[11 13] and is supported by other reports dealing with different β adrenoceptor blocking agents, either alone or in combination with some α blockade.[12 14 15] At a meeting of the International Society for the Study of Hypertension in Pregnancy in 1984, 40 abstracts dealt with antihypertensive treatment, and 27 of them concerned the administration of β adrenoceptor blockers.

In this study we analysed, in some detail, the effects of treatment on both mothers and babies. Primigravidas were analysed both as part of the whole groups and separately, as this subdivision is most likely to include a high proportion of women with hypertension associated with pregnancy (pre-eclampsia). Such patients might be expected to have a more complicated course and less satisfactory fetal outcome, although the clinical course of chronic hypertension of the severity described in this study is poor, with perinatal mortality as high as 30% in earlier reports[16] and of 8-9% in recent large multicentre studies.[17] The outcome of treatment and of pregnancy was the same in primigravidas as in the groups overall. The severity and degree of control of hypertension were the same, and, apart from a trend towards higher rates of caesarean section (which were high overall, reflecting the high risk nature of this group of pregnant women), there were no significant differences from the total group in either maternal or fetal outcome of pregnancy.

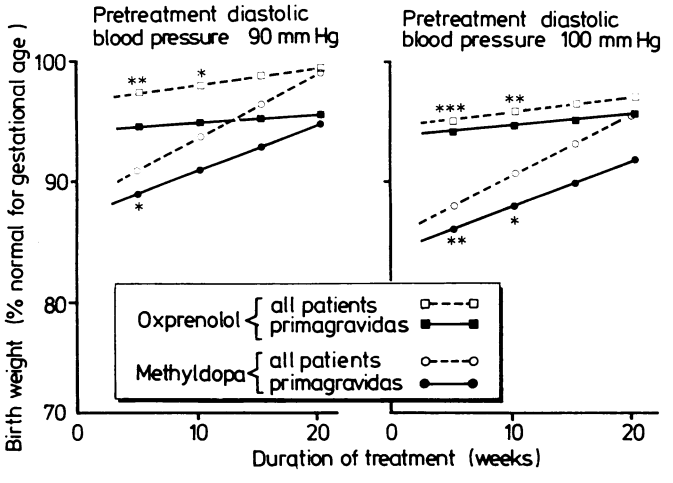
One area of concern is the superimposition of hypertension associated with pregnancy in chronically hypertensive women and its progression despite control of blood pressure. The diagnosis of this condition can be extremely difficult, as described in Pollak and Nettle's classic review of renal biopsy material.[18] Primigravidas are particularly susceptible to hypertension associated with pregnancy, but they may also have chronic hypertension, even without a relevant personal or family history. Ten women in each group in our study required urgent delivery because of the severity of their disease. All of these women had heavy and increasing proteinuria, which developed after the start of treatment in four patients given oxprenolol and five given methyldopa. This may seem a high incidence of complications but is again considerably better than the reported incidence of the development of proteinuria in untreated patients with this severity of hypertension.[17] This finding supports others reported recently after use of another β adrenoceptor blocking agent, atenolol,[12] suggesting that control of hypertension does have a preventive effect on superimposed pre-eclampsia.

In our original report, which dealt with 53 women with diastolic blood pressures of over 100 mm Hg before treatment, we found a highly significant difference between mean birth weights of babies born to women treated with oxprenolol and

those born to women treated with methyldopa (97% *v* 86% of normal for gestational age, $p < 0.001$). Although the same trend was apparent in these results, the difference between the groups was less (97% *v* 92% of normal), in part because the hypertension before treatment was less severe in both groups of women. Tables III-V show more detailed analyses of these results and cover other factors known to affect potential fetal growth. In both groups male infants were heavier at birth than female infants, and multiparous women had heavier babies than primigravidas. Although there was an overall trend in those treated with oxprenolol towards heavier babies, and thus fewer neonatal problems requiring observation in the neonatal intensive care unit, differences failed to achieve significance in some subgroups, probably because of the small numbers studied.

A study in Britain in 1983 comparing oxprenolol and methyldopa for the treatment of hypertension in pregnancy failed to confirm our earlier findings regarding birth weight,[11] although they were supported by a study in New Zealand.[13] One of the major difficulties in comparing studies of this type is non-uniformity of selection of patients and of criteria for subsequent control of hypertension. The major difference between the British study and our previous report was the therapeutic goal during the periods of treatment (diastolic blood pressure <95 mm Hg as against <85 mm Hg, respectively). It is unclear from the results presented by Fidler *et al* how well the therapeutic aim was achieved.[11] These clinical therapeutic factors may not at first appear important, but it may well be that patients reported on in that study had considerably raised blood pressures for considerable periods, even while taking antihypertensives. The administration of a therapeutic agent is not a sufficient condition for assuming therapeutic efficacy, and the degree of control of hypertension may have been a critical factor in the results that we reported earlier. The smaller differences that we report here may well represent inclusion of patients with less severe hypertension and therefore less expected retardation of intrauterine growth.

To investigate this possibility more closely the outcome variable of birth weight was analysed by multiple regression and results compared for the two treatment groups according to severity of hypertension before treatment and duration of treatment. The figure shows the results of this regression analysis, with birth weight corrected for gestational age, for the treatment groups overall and for primigravidas separately (diastolic blood pressure before treatment fixed at 90 or 100 mm Hg). These results confirm the difference between the two drugs in the effect on fetal growth that we found earlier, with significantly heavier babies in the group treated with oxprenolol. As expected, the difference was more pronounced in those with more severe hypertension and was present equally in the primigravidas and in the total group. From this analysis came another interesting and potentially valuable finding, which may explain some of the differences found in several other therapeutic studies. With increasing duration of treatment the differences between the two treatment groups became less, and after eight weeks of treatment in those with less severe hypertension (12 weeks in those with diastolic blood pressure before treatment ≥ 100 mm Hg) the differences between the two groups were no longer significant. In our preliminary report we postulated, from studies of plasma volume and haemodynamics, that the potential benefit to fetal growth from treatment with oxprenolol might be due to peripheral vasodilatation, perhaps secondary to the intrinsic sympathomimetic activity of that agent, rather than simply to control of hypertension, as this variable was controlled equally well in both patient groups. The results presented here are in keeping with that hypothesis, and we would suggest that over time a similar effect can be obtained by adequate control of hypertension, as shown by the reduction of the difference between the two groups with increasing duration of treatment. This is probably a response to adequate long term control of hypertension per se and therefore separate from the specific early vasodilatation resulting from treatment with oxprenolol.



Regression analysis of differences in birth weights (% normal for gestational age) between groups treated with oxprenolol and methyldopa, according to initial severity of hypertension (fixed at 90 or 100 mm Hg) and duration of treatment.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

It appears, therefore, that control of hypertension can be associated with good fetal growth if that control is adequate and can be continued for a sufficient period. The long term effects of treatment are probably similar to those in non-pregnant women, with some relief of vasoconstriction, some retention of salt and water, and expansion of plasma volume, although confirmation of this will require measurement of the appropriate variables.

Clearly, for short term treatment there is potential fetal benefit from treatment with oxprenolol. Twenty nine (16%) patients could have treatment for only two weeks or less, and it was during this time that the most pronounced difference was seen between the two treatment groups. As hypertension in pregnancy (whatever its underlying cause) may pursue an accelerated course, and it is uncertain in advance in which patients this is likely to occur, initial treatment with oxprenolol seems most reasonable. This would be our recommendation, provided that there is no maternal contraindication to the administration of β blocking agents.

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