THE EVALUATION OF LABETALOL IN THE TREATMENT OF HYPERTENSION COMPLICATING PREGNANCY

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1 Eighty-five women with severe hypertension complicating pregnancy were treated with oral labetalol (Trandate). Six of these had a twin pregnancy and 54 had proteinuria.

2 Effective control of the blood pressure was achieved in all but six patients. The maximum dose of labetalol prescribed was 1200 mg daily. There were no significant maternal or foetal side-effects.

3 Foeto-placental function was carefully monitored in all patients. Twenty-four of the 89 infants born alive showed evidence of intra-uterine growth retardation, the highest incidence occurring in the group of patients with essential hypertension complicated by pregnancy induced hypertension.

4 The low perinatal mortality of 4.4% was a reflection of the meticulous control of the blood pressure.

5 There were no congenital malformations or evidence of oculotoxicity in any of the infants delivered.

6 The efficient hypotensive action of orally administered labetalol together with the absence of maternal and foetal side effects and consequent improved perinatal mortality confirms that it is an eminently suitable drug for the treatment of hypertension complicating pregnancy.

Introduction

Hypertensive disease complicates approximately 10 per cent of all pregnancies. The level of blood pressure is closely related to foetal well-being and if persistently elevated it is associated with an increase in perinatal mortality and morbidity. There is still confusion amongst clinicians concerning treatment and consequently the disease accounts for significant maternal and foetal mortality and morbidity. Despite the confusion recent reports show that control of hypertension in pregnancy by antihypertensive drugs results in better survival (Michael 1975; Redman *et al.*, 1976; Michael, 1979*a*; Gallery *et al.*, 1979).

The choice of the antihypertensive drug is dependent on its efficacy when administered orally and its freedom from foetal and maternal side-effects. Many antihypertensive drugs are undesirable for use in pregnancy because of side-effects and a poor hypotensive action (Michael, 1980*a*).

The value of labetalol (Trandate) in the control of hypertension complicating pregnancy with resulting improved foetal survival has already been established (Michael, 1979*a*).

At the King Edward Memorial Hospital for Women, Perth, Australia, labetalol has been the drug of choice since 1979 for those patients with hypertensive disease in pregnancy where the foetus is too immature to consider its delivery. This decision was undertaken following clinical trials with the drug (Michael, 1979*a*), which showed that adequate reduction in blood pressure prevented any cerebral or cardiac complications of the hypertension and allowed pregnancy to safely continue until foetal maturity was reached. This resulted in a reduced foetal loss from prematurity by preventing premature induction of labour for uncontrolled hypertension in the mother.

The study now reported shows our extended experience with labetalol in 85 pregnancies where hypertension was a complicating factor.

Methods

In a previous study (Michael, 1979*a*) only patients with severe disease were included. The blood pressure in this group reached levels of 150/105 mm Hg or more before treatment was commenced. Since it is accepted that where the diastolic blood pressure is 100 mm Hg or more the risk of foetal death *in utero* is increased and that antihypertensive therapy is indicated where delivery of the foetus is not contemplated or possible. Hence patients with persistent elevation of blood pressure in excess of 160/100 mm Hg were selected for treatment with labetalol.

Eighty-five patients (six with twin pregnancy) were treated and delivered (Table 1). Fifty-four of

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Table 1 Patient details

Number of patients	85
Primigravidae	39
Age distribution	16–42 yr
Multiple pregnancy	6
Diabetes	1
Underlying renal disease	9
Proteinuria	54

these patients had proteinuria which indicated the severity of the disease treated. The blood pressure range was 160/100 to 200/135 mmHg. Thirty-two patients were known to have untreated essential hypertension and of these 12 developed superimposed pregnancy induced hypertension. The remaining 53 patients developed pregnancy induced hypertension (Table 2). In all patients treatment was commenced in the middle trimester of pregnancy and continued for a minimum of 1 week and up to a maximum of 19 weeks.

Table 2 Blood pressure details

Blood pressure range (mm Hg)	160/100–200/135
Pregnancy-induced hypertension (PIH)	53
Essential hypertension (EH)	20
EH and superimposed PIH	12
Duration of therapy	1–19 weeks

Treatment was commenced after patients were admitted to hospital during which the effects of bed rest and mild sedation on the blood pressure were assessed. Where the blood pressure remained elevated in excess of 100 mm Hg diastolic and where proteinuria appeared or persisted labetalol 100 mg orally was administered three times daily. The dose was increased on alternate days until adequate control of the blood pressure was achieved and any proteinuria was significantly reduced or disappeared. The maximum dose used was 1200 mg daily. Diuretics were not prescribed. Reduction in blood pressure to levels between 130/80 and 140/85 mm Hg was considered adequate, because of the theoretical risk of reduction in placental perfusion and consequent exacerbation of any pre-existing placental insufficiency, if lower levels were reached.

Once the blood pressure and proteinuria were controlled and the maternal condition remained stable with the absence of clinical, biochemical or ultrasonographic evidence of a worsening foeto-placental function the pregnancy continued to foetal maturity or at the latest the 38th week of pregnancy when delivery of the foetus occurred. Foetal activity charts and cardiotocography were also used to ensure that foetal well being was maintained.

Results

Effect of blood pressure and proteinuria

Effective control of the blood pressure was achieved in all but six patients. Four of these were less than 30 weeks gestation and had developed fulminating pregnancy induced hypertension with rapidly increasing proteinuria.

The average fall in systolic pressure was 34 mm Hg and in the diastolic pressure 28 mm Hg. Of the 54 patients with proteinuria 14 developed increasing proteinuria and required delivery of the foetus because of this. In the remaining 40 patients the proteinuria improved significantly and was either intermittent (11 patients) or disappeared (29 patients). Eclampsia did not occur in any of the patients.

Maternal side-effects

Side-effects of labetalol in the mother did not cause significant problems. Postural hypotension occurred in four patients, scalp tingling in two, and lethargy, headache and generalized rash in one patient. It was not necessary to discontinue the drug because of side-effects. However in one patient with scalp tingling, delivery of the foetus was necessary because of foetal hypoxia. Further tolerance of the drug by this patient may not have been possible, if the pregnancy had continued.

Renal and hepatic function

Elevation of the serum creatinine levels occurred in five patients though this was thought to be a reflection of the severity of the pregnancy induced hypertension rather than the labetalol treatment. The levels returned to normal after delivery of the foetus. Hepatic function remained normal.

Foeto-placental function

Two patients required delivery because of foetal hypoxia at 32 and 34 weeks gestation even though the hypertension was adequately controlled. Both of the infants survived. None of the 20 patients with

essential hypertension developed evidence of reduced foeto-placental function. However in the group of patients with pregnancy induced hypertension superimposed on essential hypertension seven of the 12 patients showed a reduction in plasma oestriol estimation below the mean for their respective gestation and in five of these there was reduced foetal growth demonstrated on ultrasound. In those with pregnancy induced hypertension (53 patients) ten patients showed evidence of reduced foetal well-being as indicated by these parameters of foeto-placental function. Twenty-four of the 89 infants born alive showed evidence of being small for gestational age when assessed by the neonatologist at delivery. There was an over representation of this group of infants in those patients with essential hypertension and superimposed pregnancy induced hypertension. The other 65 infants did not show evidence of intrauterine growth retardation when examined.

The six patients who developed progressive disease despite therapy required delivery because of increasing maternal blood pressure. Four of these infants did not survive. Two died in the neonatal period from pulmonary complications and two infants, both weighing less than 1000 g, were stillborn.

Foetal pulmonary maturity

Labetalol seemed to exert a beneficial effect on the development of foetal pulmonary maturity. In the early part of the trial this assessment was made by estimating the lecithin-sphyngomyelin ratio in the amniotic fluid. Later in the investigation, amniocentesis for the detection of lung maturity was only performed if indicated clinically. Eleven of the infants developed respiratory distress syndrome (RDS) and of these four died in the neonatal period (NND) as demonstrated in Table 3. Five infants developed hyaline membrane disease (HMD) and all but one of these survived. These findings would support the clinical and biochemical impression that foetal pulmonary immaturity is under represented in a group of preterm infants normally associated with a higher incidence of pulmonary hyaline membrane disease.

Method of delivery

Sixty-four infants were delivered by the vaginal route and of these 35 required forceps, two were delivered by the breech and 27 delivered spontaneously. The increased incidence of Caesarean section (32%) reflects the high risk population being treated. Labetalol did not interfere with labour nor complicate Caesarean section. Spontaneous preterm labour did not occur suggesting that myometrial irritability previously described with the use of β-adrenoceptor-blocking agents in pregnancy was not a problem. However, in those patients in whom induction of labour was performed the induction delivery interval was reduced indicating some excitory effect of the drug on the uterine musculature. (This was considered to be an advantage.)

Breast milk labetalol

Labetalol was recovered from the breast milk collected on the third post-partum day. The concen-

Table 3 Infants developing respiratory distress syndrome

Gestation period	*Birth weight*	*Cause*	*Outcome*
28	1110	Pneumonia	NND
30	1215	HMD	Alive
30	1600	Atelectasis	Alive
30	1040	Broncho-pulmonary dysplasia	NND
31	1255	HMD	NND
31	1390	HMD	Alive
31	1730	Pneumothorax	Alive
32	1050	Pneumonia	NND
33	1900	HMD	Alive
34	1895	HMD	Alive
38	1580	Aspiration	Alive

HMD, Hyaline membrane disease; NND, neonatal death.

Table 4 Fetal outcome in relation to birth weight

Birth weight	*Alive*	*Stillbirth*	*Neonatal death*	*Total*
500–1000	—	2	—	2
1000–1500	8	—	3	11
1500–2000	17	—	1	18
2000–2500	21	—	—	21
2500–3000	21	—	—	21
3000–	18	—	—	18
Total	85	2	4	91
Perinatal mortality	= 6.6%			
Corrected perinatal mortality	= 4.4%			

tration did not seem to be related to the maternal plasma levels until the higher levels of the drug were reached. Apart from one infant who had hypotension at birth probably as a result of asphyxia rather than labetalol there were no adverse effects in the infants.

Perinatal outcome

The foetal outcome in relation to birth weight is shown in Table 4. The two stillbirths weighed 720 g and 640 g respectively and occurred as a result of severe fulminating pregnancy induced hypertension. Fourteen of the infants were asphyxiated at birth and all but the infants that did not survive responded quickly to resuscitation. The total perinatal mortality was 6.6%, an excellent outcome considering the severity of the hypertension. By deleting the two previable stillborn infants from the data the corrected perinatal mortality is further reduced to 4.4%. Although previous studies have emphasized the confusion that exists in the management of hypertensive disease in pregnancy, all agree that the highest perinatal mortality (PNM) is associated with those patients who have essential hypertension together with superimposed pregnancy induced hypertension. This current study is no exception. Seventy-five per cent of the neonatal deaths occurred in this group (Table 5). The lowest perinatal mortality was associated with treated maternal essential hypertension. This is a reflection of the meticulous antenatal care these patients received throughout pregnancy and that effective early treatment of the essential hypertension prevents the occurrence of pregnancy exacerbation of the blood pressure with its associated increased perinatal mortality and morbidity.

None of the infants showed evidence of oculotoxicity or congenital malformations.

Discussion

The results of this expanded study to evaluate labetalol in pregnancy confirm the efficient hypotensive action of the drug together with its freedom from maternal and foetal complications.

In the past an increasing variety of hypotensive drugs have been used in pregnancy. Unlike this study where a single drug was effective other reports indicate the addition of another antihypertensive to control the blood pressure is frequently required. Gallery *et al.*, (1979) found it necessary to add hydrallazine to both treatment regimens of oxprenalol and methyldopa for improved blood pressure control. Multiple drug therapy confuses an already complex condition involving the mother, the foetus, the foeto-placental unit and its perfusion.

The reported effects of antihypertensive therapy on the placental circulation and therefore oxygenation of the foetus are conflicting. Gallery *et al* (1979) have suggested an improvement with oxprenalol which is reflected in the size of the infants at birth. The levels of blood pressure treated in that series can only be classified as moderate disease. Few of the patients reported had serious disease. Welt *et al.* (1981) have reported a two-thirds incidence of small, for gestation age, infants born to women on oral antihypertensive agents.

The results of the study with labetalol did not confirm the previous findings. The best perinatal mortality and largest infants at birth occurred in those patients with essential hypertension. This group was composed of patients who had received labetalol for the longest time before delivery. Perhaps the early treatment of essential hypertension does not allow the disease to reduce placental perfusion (which is known to occur in the untreated patient) as well as preventing superimposed pregnancy induced hypertension. Unlike

Table 5 PNM related to type of hypertension

	Stillbirth	*Neonatal death*	*Total*
PIH	2 (<1000 g)	1	3
EH with PIH	—	3	3
EH	—	—	—

PIH, Pregnancy-induced hypertension; EH, essential hypertension.

other antihypertensive drugs labetalol reduces peripheral resistance without significantly reducing maternal cardiac output and pulse rate. This may be an additional factor in maintaining adequate placental perfusion and therefore foetal oxygenation in the treatment of pregnancy hypertension with labetalol.

The excellent perinatal mortality of 4.4% compares extremely favourably with other studies. Redman *et al.* (1976) in their study using methyldopa excluded the severely hypertensive group of patients who had a perinatal mortality of nearly 60%. Kincaid Smith *et al.* (1966) treated 32 severely hypertensive women in pregnancy with methyldopa in whom corrected perinatal mortality was 6.2%. Methyldopa is probably the most frequently used antihypertensive drug in pregnancy. Data are accumulating to suggest that the treatment of maternal hypertension with methyldopa may reduce the head circumference of infants where the drug has been prescribed between 16 and 20 weeks gestation (Ounsted *et al.*, 1980). This may be the sensitive period for brain growth (Editorial, *Lancet*, 1979). This apparent effect on foetus head growth was not observed where the foetal has been exposed to labetalol although careful evaluation and follow up is continuing.

This expanded study confirms the previous impression that labetalol is a safe and efficient drug for use in the control of hypertensive disease complicating pregnancy. Its rapid absorption when administered orally allows an early effective reduction in blood pressure. The freedom from maternal and foetal side-effects together with the excellent perinatal outcome in a condition usually accompanied by a high maternal and foetal mortality and morbidity confirms its suitability for use during pregnancy. The low incidence of pulmonary hyaline membrane disease and the possibility that it exerts a direct beneficial effect on foetal lung maturation suggests that it is the drug of choice in the treatment of hypertensive disease arising in or complicating pregnancy.

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