

First year of life after the use of atenolol in pregnancy associated hypertension

B REYNOLDS, L BUTTERS, J EVANS, T ADAMS, AND P C RUBIN

University Department of Materia Medica and Divisions of Paediatrics and Obstetrics and Gynaecology, Stobhill General Hospital, Glasgow

SUMMARY We describe the results of a prospective study in which 120 women who developed hypertension in the last trimester of pregnancy were randomly allocated in double blind manner to atenolol or placebo. The mean duration of treatment was five weeks. The only difference between groups during the neonatal period was in respiratory distress syndrome, mainly related to spontaneous premature labour, which occurred in six placebo group babies but in none from the atenolol group. Fifty five children from each group have been followed to 1 year of age. All in the atenolol group are developing normally but one child from the placebo group is brain damaged. These findings do not suggest any short or medium term paediatric complications after the use of beta blockers in pregnancy.

Beta adrenoceptor antagonists have become widely accepted in general medical practice. Their introduction to obstetrics, however, has been accompanied by concern about a wide range of adverse effects largely affecting the fetus and neonate. These drugs have been implicated in the production of growth retardation of the fetus¹ and have had ascribed to them a considerable range of neonatal problems including hypoglycaemia, hyperbilirubinaemia, bradycardia, respiratory depression, and death.²⁻⁸ The precise relation between these complications and drug administration was difficult to evaluate because of the anecdotal or retrospective nature of observations in patients who had major disorders of pregnancy.⁹ We have recently completed a placebo-controlled evaluation of the beta blocker atenolol in women with pregnancy associated hypertension¹⁰ and describe here the findings of paediatric follow up to 1 year of age.

Methods

One hundred and twenty women who developed a blood pressure of between 140/90 and 170/110 mmHg on two occasions 24 hours apart during the last trimester of pregnancy were randomly allocated in double blind manner to treatment with atenolol or placebo. The maximum dose of atenolol was 200 mg per day and the average duration of treatment was five weeks. No other antihypertensive medication was prescribed. All babies were admitted to the

special care nursery where they had a detailed clinical examination including measurement of weight, length, occipitofrontal circumference, triceps and subscapular skinfold thickness, together with assessment of gestation by the Dubowitz method.¹¹ The results of biochemical, haemodynamic, and pharmacokinetic measurements made during this period have previously been reported.^{10 12} Infants were subsequently seen at 3, 8, and 12 months of age when a Denver development screening test was performed and growth indices were recorded. At all stages of assessment the investigator performing the evaluation was unaware of treatment category.

Data are presented as mean (standard deviation) and analysis is by intention to treat. Continuous variables recorded in the neonatal assessment were compared by unpaired two sided *t* test and in the subsequent paediatric follow up by repeated measures analysis of variance. Categorical variables were compared by analysis of contingency (χ^2).

Results

There were no major congenital malformations in either group. Two babies from the placebo group had abnormalities on clinical examination at birth: one congenital dislocation of the hip and one patent ductus arteriosus. Four babies had abnormal examinations in the atenolol group: two had congenital dislocation of the hip and two minor glandular

hypospadias. In all cases the abnormalities resolved without medical intervention. Clinical indices at birth are shown in Table 1.

Respiratory distress syndrome requiring ventilation occurred in six babies from the placebo group but in none from the atenolol group ($P < 0.05$). The reasons for delivery in these six babies were spontaneous premature labour (4), caesarian section for fulminating pre-eclampsia (1), and caesarian section because of spontaneous premature labour and bad obstetric history (1).

Fifty five babies from each group attended for follow up examination through to 1 year of age. Clinical examination was normal by 12 months in all children who had defects identified at birth. Three children from the placebo group had less than a normal score on the Denver development screening test. Two were graded as 'doubtful' at 8 months but were classified 'normal' at both 3 and 12 months. One of these was born at term but was below the

10th centile for weight and length and had bradycardia for the first 12 hours of life. The second was born at 39 weeks' gestation after induction of labour because of maternal hypertension, and showed signs of cerebral irritation for two days. The third child was definitely abnormal at all three follow up visits. She was born by caesarean section after spontaneous premature labour at 35 weeks, was below the fifth centile for weight, length, occipitofrontal circumference, and was slow to establish respiration, and was nursed in oxygen for 48 hours. Clinical evaluation at 12 months of age confirmed the presence of a spastic quadriplegia with a severe pseudo-bulbar palsy. All children in the atenolol group were graded as normal on Denver development screening test at all stages of follow up. The remaining clinical indices at 3, 8, and 12 months of age are shown in Table 2. There were no further differences between the groups.

Discussion

Maternal morbidity and mortality now represent rare complications of hypertensive pregnancy and therapeutic intervention is directed largely at the fetus. There has been increasing use of anti-hypertensive drugs in all forms of pregnancy hypertension during recent years.¹³ Among the various drugs used, methyldopa has been shown to be effective in lowering blood pressure¹⁴ and safe for the fetus^{15 16} but maternal side effects necessitated stopping treatment in 14.5% of women.¹⁴ Beta blockers have been shown to have similar efficacy to methyldopa in lowering blood pressure¹⁷ but have been held responsible for a wide range of fetal and neonatal adverse effects.⁹ Since beta blockers are used only in pregnancies having a major complication, usually severe hypertension, it can be very difficult to differentiate drug effects on the fetus from those caused by the disease. Such difficulties are overcome by a placebo controlled and double blind design as used in this study.

We have previously described the absence of adverse biochemical effects of atenolol in the neonatal period.¹⁰ The further data presented here provide no support for a harmful effect of beta blockers on the fetus or neonate, with both acute and long term clinical problems being concentrated in the placebo group. The largest single aetiological factor in morbidity was spontaneous premature labour, accounting directly or indirectly for five cases of severe respiratory distress syndrome and the one case of chronic disability. It seems unlikely that a beta-1 adrenoceptor antagonist such as atenolol would directly influence uterine motility, and the most reasonable inference to draw is that

Table 1 Clinical indices at birth (values mean (SD))

	Placebo group	Atenolol group
Length (cm)	48.6 (3.0)	48.6 (2.7)
Occipitofrontal circumference (cm)	33.9 (2.0)	33.8 (1.7)
Dubowitz: neurological	27 (3.6)	27.4 (2.7)
Dubowitz: morphological	25.1 (4.6)	26.6 (3.9)
Gestational age (weeks)	38.5 (2.1)	39.1 (1.5)
Triceps thickness (mm)	4.3 (1.2)	4.1 (1.0)
Subscapular thickness (mm)	4.5 (1.4)	4.4 (1.3)

Table 2 Clinical indices at 3, 8, and 12 months of age (values mean (SD))

	Placebo group	Atenolol group
Weight (kg)		
3	5.59 (0.76)	5.72 (0.76)
8	8.07 (0.89)	8.37 (0.86)
12	9.58 (0.97)	9.64 (1.19)
Length (cm)		
3	60.2 (3.0)	59.8 (2.6)
8	68.9 (2.6)	68.7 (2.1)
12	72.4 (2.4)	72.7 (2.3)
Occipitofrontal circumference		
3	40.8 (1.3)	40.5 (1.2)
8	45.0 (1.4)	44.6 (1.2)
12	46.8 (1.2)	46.6 (1.4)
Triceps thickness (mm)		
3	6.8 (1.2)	6.9 (1.2)
8	8.5 (1.2)	8.2 (1.2)
12	8.5 (1.3)	8.6 (1.2)
Subscapular thickness (mm)		
3	6.7 (1.2)	6.7 (1.2)
8	6.9 (1.2)	7.1 (1.2)
12	7.2 (1.3)	7.3 (1.2)

poor blood pressure control was responsible for the premature labour.

These findings relate to a consecutively recruited series of patients attending the obstetric unit of a district general hospital. They serve to emphasise the importance of good blood pressure control in relation to pregnancy outcome. These data, however, do not suggest that beta blockers used during the last trimester are likely to be associated with major fetal, neonatal or paediatric adverse effects.

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Correspondence to Dr P C Rubin, University Department of Materia Medica, Stobhill General Hospital, Glasgow, G21 3UW.

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