ATENOLOL IN THE TREATMENT OF PREGNANCY-INDUCED HYPERTENSION

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1 The pharmacological properties of atenolol suggest its possible usefulness in pregnancy-induced hypertension. The pharmacokinetics of atenolol in the pregnant woman, concentrations in cord blood, and its effects on maternal blood pressure and the foetus, are evaluated.

2 We studied 13 pregnant women with hypertension, most of them uncontrolled on methyldopa. Whole blood concentrations and urinary excretion of the drug were measured over 24 h following a 100 mg dose. Effects on maternal blood pressure, pulse rate and foetal heart rate and cardiotocograph were compared for the 4 days before treatment and the first 4 days of treatment. The birth weights and Apgar scores of the babies were recorded.

2 The pharmacokinetics of atenolol (plasma half-life of about 8 h) in pregnant women do not differ from the findings in the non-pregnant. The levels of atenolol in the cord blood were confirmed as approximately equal to those in the maternal blood.

4 In the ten women in whom blood pressure was assessed a small significant fall in blood pressure was observed.

5 A 5% mean fall in foetal heart rate resulted but in no case was a rate below 120 beats/min recorded. There was no evidence of depression of the stress response of the foetal heart. Apgar scores 5 min post partum were satisfactory.

6 Atenolol appears to be safe for use in hypertensive pregnancies. Its effectiveness as an antihypertensive agent in pregnancy requires further controlled evaluation.

Introduction

Atenolol is cardiosselective β -adrenergic receptor blocking agent which is now well established as an antihypertensive drug, the optimal dose being 100 mg once daily (Zacharias *et al.*, 1977; Dollery, 1977). It is a relatively polar, hydrophilic compound which is not metabolised, and its chemical and pharmacological properties suggest that it may be suitable for treatment of hypertension of pregnancy.

It has been shown to cross the placental barrier (Melander *et al.*, 1978) but possible effects on the foetus have not been evaluated.

The present study aims to determine the pharmacokinetics of atenolol in the pregnant woman, to confirm concentrations in the umbilical venous blood, and to evaluate the effect on maternal blood

pressure, foetal heart rate and foetal well being assessed by cardiotocography and foetal movements.

Methods

In all, 13 mothers with severe pre-eclampsia were studied, with age ranging from 21 to 33 years. The details of these patients are shown in Table 1. Pharmacokinetic studies were performed in 11 of these. All had been taken atenolol for a minimum of 4 days.

Ten of the patients were studied for antihypertensive effect. All of these were in the last month of gestation.

Table 1 Details of patients

Patient	Age (years)	Parity	Gestational age at entry (weeks)	Concurrent medication
SK	31	3	35	Methyldopa 1000 mg daily
SH	21	0	35	—
SB	22	0	37	Methyldopa 1000 mg daily
CS	28	0	38	Methyldopa 1000 mg daily
DH	29	0	36	Methyldopa 2500 mg daily
CP	32	0	35	Methyldopa 2500 mg daily
PC	30	3	36	Methyldopa 1000 mg daily
MS	32	0	37	—
SG	33	0	22	Hydralazine 75 mg daily
BM	24	1	37	—
PF	34	0	22	—
JS	33	0	38	Methyldopa 1000 mg daily
JA	21	0	33	Methyldopa 1500 mg daily

There was a 4 day 'run-in' period for all patients, during which maternal pulse and blood pressure, foetal heart rate, movements and cardiotocograph (CTG) were monitored. [The 6 point cardiotocographic score (Pearson & Weaver, 1978) has been shown to give reliable assessment of foetal well being and response to stress, the higher the score, the better the foetal well being and response to stress: it is derived from three variables, base-line foetal heart rate (FHR), response of FHR to Braxton-Hicks contractions and to foetal movements]. Blood biochemical analysis was performed, with full blood count, platelets and reticulocyte counts and FDP.

(i) Pharmacokinetic study

On day 5, a 24 h urine collection was started, a 100 mg tablet of atenolol given and simultaneously a 4 ml sample of maternal blood was taken for estimation of atenolol, frozen at -20°C and stored until analysis. Further blood samples were taken at intervals of 1, 3, 8 and 24 h. The samples were assayed for atenolol by a modification of the gas chromatographic method of Scales & Copsey (1975).

Immediately after the third stage of labour, venous blood samples were taken from the mother and the umbilical cord. These were also stored and analysed as above.

(ii) Clinical study

Maternal pulse and sitting blood pressure, and foetal heart rate, cardiotocograph and movements were recorded for a minimum of 4 days during which 100 mg of atenolol was given at 10.00 h daily. Diastolic pressure was defined by Phase V of the Korotkoff sounds.

At delivery, the birth weight of the baby, and 1 and 5 min Apgar sounds were recorded.

Results

(i) Pharmacokinetic study

As illustrated in Figure 1 the mean peak blood concentration, following the 100 mg oral dose, was $0.59 \pm 0.09 \mu\text{g/ml}$ 3 h after administration and the area under the curve over the dosing interval was $7.1 \pm 0.7 \mu\text{g ml}^{-1} \text{ h}$. The half-life was $8.1 \pm 0.5 \text{ h}$ and the 24 h urinary excretion $52 \pm 9 \text{ mg}$, indicating approximately 50% absorption. These values all lie within the normal range for non-pregnant subjects (Conway *et al.*, 1976; Brown *et al.*, 1976). The average maternal blood concentration of atenolol was $0.26 \pm 0.5 \mu\text{g/ml}$; the average cord blood concentration of atenolol was $0.22 \pm 0.13 \mu\text{g/ml}$, all samples being taken at an average time of 16.8 h after the last dose of atenolol.

Atenolol was detected in the umbilical venous blood in all cases except for SH who received 50 mg of atenolol 28 h before delivery. Unfortunately no maternal sample was obtained for comparison.

The mean maternal-foetal concentration ratio was 1:0.9 (s.d. 0.6) indicating approximately equal levels in the maternal and foetal circulations.

Figure 1 Mean atenolol maternal blood levels ($\mu\text{g/ml}$) after 100 mg once daily chronic oral dosing. $\text{AUC}_{0 \rightarrow 24} = 7.1 \pm 0.7 \mu\text{g ml}^{-1} \text{ h}$, $T_{1/2} = 8.1 \pm 0.5 \text{ h}$, 24 h urinary clearance $52 \pm 9 \text{ mg}$.

Table 2 Daily cardiotocograph scores in pre-treatment phases

Patient	CTG score—pre-treatment	CTG score—treatment
DH	5, 5	5, 4, 6
MS	6, 5	4, 6
CS	6, 6, 6	6, 5, 4, 6, 6
SB	3, 5, 5, 4, 5	6, 2, 5
BM	5, 4, 5	6, 6, 6
CP	6, 5, 5, 6	4, 6, 5, 5, 5
SH	4, 4	3, 4, 5, 5
JS	Not recorded	6, 5, 4, 5, 6
PC	Not recorded	6, 6, 6, 6
SK	Not recorded	4, 4, 3, 5

Key

Scoring system

Baseline FHR	Score
Normal range of 120 to 160 beats/min	2
Tachycardia to 180 beats/min or bradycardia to 100 beats/min	1
Tachycardia about 180 beats/min or bradycardia below 100 beats/min	0
FHR response to foetal movements	
Acceleration of at least 15 beats/min in FHR with movements	2
FHR remained unaltered in response to movements	1
Those who did not move during 30 min exposure to Doppler ultrasound	0
FHR response to Braxton-Hicks contractions (B-H)	
Acceleration of FHR with B-H contractions	2
No change in FHR with B-H contractions	1
Deceleration of FHR with B-H contractions	0

(ii) Clinical study

(a) **Maternal** There were no reported adverse effects to atenolol and no haematological abnormalities were detected. The mean fall in blood pressure was only slight though statistically significant (Wilcoxon signed rank test – $P < 0.05$): from 135.8/91.3 to 133.2/89.5 mmHg. The mean resting heart rate fell from 83.0 to 78.1 beats/min ($P > 0.05$).

(b) **Foetal** No foetal heart rate (FHR) of less than 120 beats/min was recorded. The mean fall of 7.4 beats/min (5.4%) from 137.4 to 130.0 was statistically significant ($P < 0.01$).

Pre-treatment and treatment cardiotocographic (CTG) scores are shown in Table 2. It is evident that the drug is not affecting the foetus in an adverse way. Table 3 lists relevant maternal and foetal information during the perinatal period. Eight of the mothers had taken atenolol for 1 week or less, and only two for more than 3 weeks. The indications for interventive delivery were related to maternal hypertension in six cases. Other indications were placenta praevia ($n =$

2), foetal distress ($n = 2$) and breech with poor obstetric history ($n = 1$). The birth weights are consistent with severe pre-eclampsia, with all except one of the babies being below the 50th percentile of birth weight for sex and gestational age; three were below the 10th percentile. All the babies had good Apgar scores except for one in whom prematurity (33 weeks) would have had the major effect; this baby survived and was well at 6 months.

Discussion

(i) Pharmacokinetics

The physiological changes in plasma volume, metabolism and excretion which occur in pregnancy may be expected to affect the pharmacokinetics of drugs. We therefore felt that before any evaluation of anti-hypertensive effect of atenolol in pregnancy could be made, we should ensure that such an effect would reasonably be expected in the light of any change in pharmacokinetics. Our results showed no difference from the non-pregnant state in blood levels and urinary excretion of atenolol.

Concentrations of atenolol found in the umbilical venous blood confirm the results of Melander *et al.* (1978), in being approximately equivalent to maternal concentrations. Truelove *et al.* (1973) found a correlation between the lipid solubility of β -adrenoceptor blockers and permeability of the placenta to the compound in the ewe. On these grounds, atenolol, which has a very low lipid solubility, might be expected not to cross the placenta, or to be found at very low concentrations in the neonate. This would also be expected of sotalol, but O'Hare *et al.* (1979) also found approximately equal concentrations of drug in umbilical and maternal venous blood. Metoprolol and propranolol are lipophilic and would perhaps be expected to reach higher levels in the foetus. However, Sandstrom (1978) demonstrated approximately equal concentrations of metoprolol in neonatal jugular venous blood and maternal blood. Thus other factors may be important, such as the degree of plasma protein binding; atenolol is only 3% bound in contrast to 80–90% binding of propranolol (Barber *et al.*, 1978).

(ii) Safety

Care must be exercised in the interpretation of pharmacokinetic data in the foetus and neonate. Clinical findings are clearly more relevant to safety and may give a better reflection of drug distribution than the blood concentrations we are able to measure.

Doubt has been cast on the safety for the foetus of β -adrenoceptor blockade during pregnancy in case

Table 3 Summary of outcome of labour in 13 patients of atenolol

Patient	Number of days on atenolol	Mode of delivery	Indications for intervention	Intra partum foetal distress	Sex	Length ² of gestation (weeks)	Apgar score 1 min 5 min	Birth weight (kg)	Child Tenth percentile of birth weight for sex and gestational age (kg)
SK	5	LSCS	Placenta praevia	-	F	36	5 9	2.120	2.055
SH	4	LSCS	Breech, severe P.E.T.	-	M	36	3 8	1.985	1.935
SB	3	LSCS	Maternal hypertension and foetal distress	+	F	38	9 10	2.530	2.527
CS	14	ND	—	-	M	40	8 10	2.750*	2.867
DH	5	F	Foetal distress	+	M	37	9 10	2.840	2.383
CP	21	ELSCS	Maternal hypertension	-	M	38	8 10	2.500*	2.553
PC	11	ND	—	-	F	38	9 10	3.085†	2.527
MS	4	ELSCS	Hypertension and proteinuria	-	F	38	4 8	3.200	2.527
SG	119	LSCS	'Doubtful' CTG	±	M	39	8 9	2.690*	2.782
BM	4	LSCS	Uncontrolled hypertension	-	F	37	7 9	2.750	2.193
PF	102	LSCS	Placenta praevia diminishing foetal movements	-	M	36	4 9	2.555	2.194
JS	7	ELSCS	Breech, poor obstetric history	-	M	39	7 10	3.075	2.782
JA	3	LSCS	Severe toxemia low oestriol level flat CTG	+	F	33	3 6	1.474	1.350

¹LSCS = emergency lower segment caesarian section

ELSCS = elective lower segment caesarian section

ND = normal delivery

F = forceps

2 = gestational age confirmed by scan

* = birth weight below tenth percentile for sex and gestational age

† = birth weight above the fifth percentile for sex and gestational age

reports by Gladstone *et al.* (1975), Cottrill, *et al.* (1977) and Habib & McCarthy (1977), and in a retrospective study by Liebermann *et al.* (1978). These have all related to propranolol and include reports of placental insufficiency, neonatal hypoglycaemia, respiratory depression and severe bradycardia. However, maternal and neonatal blood concentrations in these and other studies have shown considerable variability (Langer *et al.*, 1974) and clinical effects may be found, apparently out of proportion to maternal and foetal blood concentrations.

The lipid soluble propranolol and metoprolol are almost wholly metabolised by the liver (Johnsson & Regardh, 1976) and it may be that the immature neonatal liver is unable to cope with concentrations present after delivery, leading to accumulation during the next 3–4 h. Protein binding may also complicate the situation.

We have observed a fall in foetal heart rate of approximately 5% in all but two of our cases treated with atenolol. Thus the pharmacokinetic findings are supported by clinical evidence of β -adrenoceptor blockade. In order to assess the clinical significance of this result we have examined both the ante partum and intra-partum foetal cardiocytographs, and the indications for interventive delivery. All the babies with the exception of one, which was 7 weeks premature, had 5 min Apgar scores of 8, 9 or 10 and in the light of all these measured indicators, we conclude that there was no depression of the response of the foetal heart to stress in mothers taking atenolol.

(iii) Efficacy

Atenolol produced only a small but significant fall in blood pressure when added to methyldopa in this

study. This was a little surprising as atenolol is known to be at least as good an antihypertensive agent as methyldopa, with the combination of these two drugs being more effective than either given alone (Webster *et al.*, 1977). Indeed an ongoing randomised, prospective study (by the authors) comparing atenolol and methyldopa in pregnancy-induced hypertension confirms that atenolol is an effective antihypertensive agent being at least as effective as methyldopa. The efficacy of atenolol in the treatment of severe pre-eclampsia has already been described (Lunell *et al.*, 1979), albeit in a small number of patients. We are therefore left to explain the relative lack of efficacy of atenolol in the present study. Most of the patients had been poorly controlled on methyldopa and had received atenolol for only a few days prior to delivery. Thus the present group might be considered unsuitable for the assessment of efficacy of atenolol. There is no theoretical reason why atenolol should not be a suitable antihypertensive agent for pregnant patients, as has been the case for other β -adrenoceptor blockers such as oxprenolol (Gallery *et al.*, 1979), propranolol (Eliahou *et al.*, 1978), labetalol (Lammings & Symonds, 1979) and metoprolol (Sandstrom, 1978).

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