CIRCULATORY AND METABOLIC EFFECTS OF A COMBINED α - AND β -ADRENOCEPTOR BLOCKER (LABETALOL) IN HYPERTENSION OF PREGNANCY

NILS-OLOV LUNELL, PAUL HJEMDAHL, BERTIL B. FREDHOLM, HENRY NISELL, BENGT PERSSON & JAN WAGER

Department of Obstetrics and Gynaecology, Huddinge University Hospital, Department of Pharmacology, Karolinska Institutet and Department of Pediatrics, St Göran's Hospital, Stockholm, Sweden

1 Seven women with hypertension of pregnancy were given the combined α - and β -adrenoceptor blocking drug labetalol (50 mg i.v.) in their last trimester. Acute effects were studied for 3 h after administration.

2 Systolic and diastolic blood pressures were significantly reduced from 143 ± 4 (s.e. mean) to 127 ± 5 mmHg and from 101 ± 2 to 88 ± 2 mmHg, respectively. Maternal heart rate fell significantly from 77 ± 5 to 68 ± 3 beats/min. The changes remained during the 3 h of observation. Foetal heart rate was not affected. No side-effects were encountered.

3 Plasma noradrenaline increased significantly from 1.54 ± 0.16 to a peak value of 2.37 ± 0.41 nmol/l suggesting sympathetic activation following labetalol. Plasma adrenaline levels were essentially unchanged. Plasma glucose, insulin and C-peptide showed only minor changes. No major effects on lipid metabolism were seen except a significant fall of nonesterified fatty acids at 60 min. Plasma cyclic AMP increased significantly throughout the observation period, perhaps indicating β -adrenoceptor agonist activity of labetalol.

4 The effectiveness of labetalol as an acute hypertensive agent together with apparent absence of metabolic disturbances and other side-effects makes it an interesting drug for the treatment of hypertension during pregnancy.

Introduction

There is some evidence that β -adrenoceptor blocking agents may be useful in the treatment of hypertension in pregnancy. For example the β_1 -selective agent metoprolol was found to produce good blood pressure control with lower perinatal mortality and foetal growth retardation than seen with hydralazine (Sandström, 1978). Gallery *et al.* (1979) observed that the non-selective β -adrenoceptor blocking agent oxprenolol appeared safe and effective in controlling hypertension during pregnancy. On the other hand, there is evidence that the non-selective β -adrenoceptor antagonist, propranolol, which in contrast to oxprenolol lacks β -adrenoceptor agonist activity, may cause intrauterine growth retardation (Pyrn, Phelan & Buchanan, 1979) and high perinatal mortality (Lieberman *et al.*, 1978) although others have not found these deleterious effects (Tcherdakoff *et al.*, 1978; Eliahou *et al.*, 1978). Thus β -adrenoceptor blocking agents have different properties due to differences in selectivity and intrinsic activity.

Hypertension of pregnancy is characterized by an increased peripheral vascular resistance (Bucht & Werkö, 1953; Ginsburg & Duncan, 1967) and an

increased pressor response to noradrenaline (Talledo, Chesley & Zuspan, 1968). Noradrenaline also causes uterine vasoconstriction due to stimulation of α -adrenoceptors (Ladner *et al.*, 1970). The possibility therefore exists that combined α - and β -adrenoceptor blockade may be especially useful in the treatment of pregnancy hypertension. Labetalol is an effective antihypertensive drug (Prichard *et al.*, 1975; Bolli *et al.*, 1977) which combines α - and β -adrenoceptor blocking properties (Richards & Prichard, 1979) and also appears to possess β -adrenoceptor agonist activity (Carey & Whalley, 1979; Riley, 1980).

In the present report we have studied the acute effects of labetalol on circulatory and metabolic parameters and plasma catecholamines in patients with mild to moderate pregnancy hypertension.

Methods

Seven women in their last trimester of pregnancy and with hypertension, defined as a blood pressure equal to or above 140/90 mmHg, were studied. Clinical data

Table 1 Clinical data on patients and offsprings

Subject	Mother				Time between test-delivery (days)	Infant		Neonatal outcome
	Prepregnancy weight (kg)	Weight-gain (kg)	Blood pressure (before test)	Protein-uria (g)		Birth weight (g)	Apgar score 1' 5'	
1	60	13	135/100	0	3	2790	6 8	normal
2	80	9	135/95	0	7	3130	9 10	normal
3	54	23	140/95	++	3	4150	9 10	normal
4	55	17	140/100	0	3	3720	9 10	normal
5	68	4	140/105	0	8	2930	6 8	normal
6	67	3	145/105	5.2	31	1450	9 10	SFD*
7	67	12	165/105	+	21	2520	8 10	normal

* small for date infant

for mothers and infants are given in Table 1. The patients were in the left supine position and blood sampled from an indwelling catheter in a brachial vein. After a resting period of 20 min zero-time values were obtained. Labetalol (50 mg) was injected slowly (10 min) and blood samples were withdrawn at 20, 40, 60, 120, and 180 min. Catecholamines and cyclic AMP were determined on plasma from blood samples (10 ml) drawn into ice cold tubes containing EDTA (10 mM final concentration). Blood samples for glucose, insulin, C-peptide, non-esterified fatty acid (NEFA) and 3-hydroxy-butyrate (3-HB) were drawn into ice cold heparin containing tubes. After centrifugation (in the cold for catecholamines and cyclic AMP) plasma was stored frozen (-80°C for catecholamine samples) until assayed.

Blood pressure and maternal and foetal heart rates were determined every 10 min during the first hour and thereafter at 120 and 180 min. After this study the women were given hydralazine until delivery.

Chemical determinations

Plasma catecholamines were assayed by high performance liquid chromatography with electrochemical detection described and validated elsewhere (Hjemdahl, Daleskog & Kahan, 1979). Cyclic AMP, C-peptide, insulin, glucose, glycerol, 3-HB and NEFA were determined as described elsewhere (Fredholm *et al.*, 1978).

Results

Following labetalol administration both systolic and diastolic blood pressure fell significantly (Figure 1a). These changes were present already at the end of the 10 min infusion. The lowest values were observed after 30–40 min, when systolic blood pressure had fallen from 143 ± 4 (mean $\pm$ s.e. mean) to 127 ± 5 mmHg ($P < 0.001$) and diastolic blood pressure from 101 ± 2 to 88 ± 2 mmHg ($P < 0.002$). Maternal heart rate decreased significantly from 77 ± 5 to 68 ± 4 beats/min ($P < 0.05$) after 50–60 min. The blood pressure remained significantly reduced at 180 min and maternal heart rate at 120 min. There was no change in foetal heart rate.

After labetalol injection plasma noradrenaline increased from 1.54 ± 0.16 nmol/l to a peak value of 2.57 ± 0.41 nmol/l ($P < 0.05$, Figure 1b) at 20 min. After the first hour no significant elevation of plasma noradrenaline was observed. Plasma adrenaline levels were essentially unchanged.

Labetalol (up to 1 ng/ml unextracted solution) did not interfere with the plasma catecholamine assay. However, we regularly obtained two extra peaks located between dopamine and the internal standard, α -methyldopamine, in the chromatograms. Occasionally one of these peaks interfered with

Figure 1 (a) Mean changes in maternal blood pressure and maternal (MHR) and foetal (FHR) heart rate after 50 mg labetalol i.v. (b) Changes in plasma adrenaline (A) and noradrenaline (NA) and (c) Changes in plasma cyclic AMP. Values are given as mean $\pm$ s.e. mean * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$. $\uparrow$ indicates time of labetalol injection.

dopamine, the values for which are therefore not given. These unidentified peaks may represent metabolites of labetalol.

Throughout the observation period cyclic AMP showed a small but significant increase from 8.2 ± 1.5 nmol/l to a maximum of 11.5 ± 1.5 nmol/l (Figure 1c).

There were very slight changes in the plasma levels of insulin, C-peptide, glycerol, and 3-HB. Plasma glucose increased insignificantly between 20 and 60 min.

A significant fall was observed in the levels of NEFA from 1.09 ± 0.16 to 0.91 ± 0.10 nmol/l ($P < 0.05$) at 60 min after labetalol. No side-effects of the labetalol injection occurred in these women who remained in the supine position throughout the study.

Discussion

The present investigation shows that a slowly injected 50 mg dose of labetalol produces an adequate anti-hypertensive response without side-effects in the supine patient with pregnancy hypertension. Thus, systolic and diastolic blood pressure and maternal heart rate were lowered whereas foetal heart rate was unaffected. The hypotensive response lasted for at least 3 h.

The hypotensive response in our patients was accompanied by an increase in plasma noradrenaline as shown earlier in essential hypertension (Christensen *et al.*, 1978). This is presumably due to baroreceptor reflex induced activation of sympathetic nerve. The increase in plasma noradrenaline was transient and of modest magnitude and is probably not of any major importance.

Since β -adrenoceptor blocking agents have metabolic effects (e.g. Day *et al.*, 1979) we studied indices of carbohydrate and lipid metabolism. Labetalol had only minor effects on carbohydrate metabolism as glucose, insulin and C-peptide were essentially unchanged.

Similarly, lipid metabolism appears to be little altered by labetalol. On the other hand plasma cyclic AMP increased after labetalol which may be explained by partial β -adrenoceptor agonist activity of the compound (Carey & Whalley, 1979; Riley, 1980) or by active metabolites of labetalol. The presence of such metabolites is also suggested by the poor correlation between plasma concentrations of labetalol and the hypotensive effect (McNeil *et al.*, 1979) and perhaps by our chromatographic findings. As noted in the introduction labetalol may have haemodynamic advantages over e.g. propranolol in pregnancy hypertension where utero-placental flow is of special importance for foetal outcome. The present results indicate a good therapeutic effect of labetalol in pregnancy hypertension with only minor influences on metabolism and sympathetic activity.

Taken together with results from other recent reports (Lamming & Symonds, 1979; Michael, 1979) this makes labetalol an interesting alternative in the treatment of pregnancy hypertension.

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