The effect of nifedipine on fetal umbilical artery Doppler waveforms in pregnancies complicated by hypertension

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Summary

The effect of nifedipine 5 mg administered sublingually to pregnant hypertensive patients was examined in a randomised controlled double-blind study. The effect on maternal blood pressure and the fetal umbilical artery Doppler waveform was studied for 30 minutes before and 30 minutes after administration of the drug or placebo. This dose resulted in a significant drop in maternal blood pressure 30 minutes after administration and did not result in a significant change in the Doppler umbilical artery waveform (in fetuses with normal waveforms) when compared with a control group.

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Nifedipine is a pyridine derivative and is one of the most potent of the calcium entry blockers. Despite having been used extensively in obstetrics, both for the treatment of severe pregnancy-associated hypertension[1] and to suppress preterm labour,[2] the fetal effects of the drug have not been fully elucidated. The effect on the fetal circulation must be studied before nifedipine can become accepted for use in pregnant patients.

Doppler ultrasound velocity waveforms recorded from the umbilical artery can be used to assess fetal well-being[3] and give information on the fetal circulation. Pulsed Doppler ultrasound evaluation is an indirect way of measuring blood volume flow and velocity; it has an accepted daily variability[4] and is a relatively simple method of clinical investigation.

This clinical experiment was designed to see if administration of nifedipine or a placebo changed the umbilical artery waveform characteristics, thus giving information on any possible fetal effects.

Subjects and methods

Nineteen hypertensive pregnant women who were > 28 weeks pregnant were studied. All patients gave written, informed consent to the study, which was approved by the University of Cape Town Ethics Committee. The inclusion criteria required that singleton pregnancies with reactive non-stress tests were studied. Hypertension was defined as a mean diastolic blood pressure, taken over four 6-hourly readings with a standard mercury sphygmomanometer, ⩾ 90 mmHg. The patients were then randomly allocated to receive nifedipine 5 mg or a placebo by virture of the last digit of their folder number.

The nifedipine was administered sublingually as a single 5 mg dose, the placebo capsule was a similar size and contained vitamin syrup. The ultrasonographer and patient were unaware which capsule had been given.

Patients were examined supine on the ultrasound couch with 30° lateral tilt. Ten minutes were allowed before starting the study to reassure the patient. Blood pressure recordings were taken at 5-minute intervals from 0 to 60 minutes using the Critikon Dinamp Vital Signs Monitor (18465X). Fetal umbilical artery waveform patterns were measured using the Aloka Doppler Unit (UGR-34) with a 100 Hz filter at 10-minute intervals from 0 to 60 minutes. The umbilical artery was identified with a B-mode scanner and the sample volume placed over the vessel; each Doppler trace had an umbilical vein tracing throughout. The Doppler trace was observed until a constant signal was obtained and the A and B values were measured from one representative waveform. The waveform was one of five waveforms that were uniform and a photograph was taken to check that it was representative. Adjacent waves were sampled to ensure uniformity. The Pourcelot ratio[5] was calculated from the A and B values (Fig. 1) using standard calipers; it was not corrected for fetal heart rate, since the rate was in the normal range (120 - 160/min) in every patient except case 3 in the nifedipine group and there was no shift > 20/min in any patient. Normalisation of the ratio for heart rate was unnecessary under these circumstances.[6]

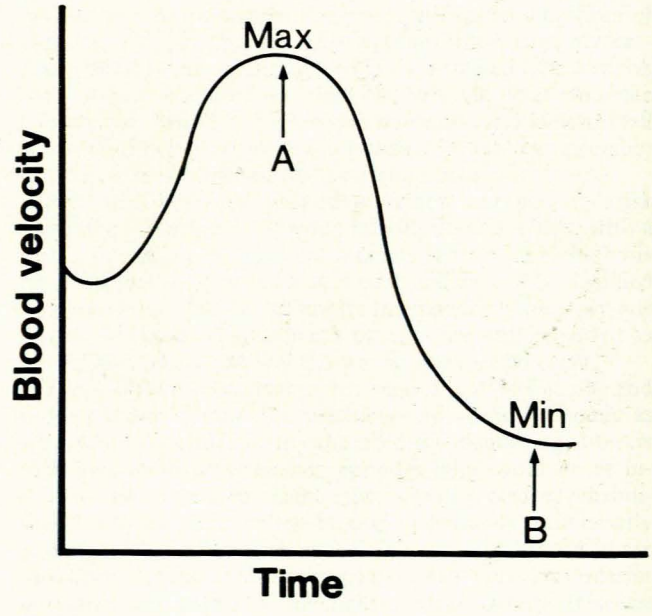

Fig. 1. Pourcelot ratio: $\frac{A - B}{A}$. Definition of Pourcelot ratio from one umbilical artery waveform.

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Results

The characteristics of the two groups of patients are shown in Tables I and II. The Mann-Whitney non-parametric *U*-test showed no significant difference between the two groups ($P > 0,05$) with respect to gestational age, height and weight.

TABLE I. NIFEDIPINE GROUP COMPARED WITH PLACEBO GROUP FOR GESTATIONAL AGE, WEIGHT AND HEIGHT (MEAN ± SD)

	Nifedipine group (N = 11)	Placebo group (N = 9)	Mann-Whitney non-parametric *U*-tests between means
Gestational age (wks)	**34,5 ± 2,7**	**35,1 ± 3,6**	**NS**
Height (cm)	**159,2 ± 3,4**	**157,4 ± 4,7**	**NS**
Weight (kg)	**72,2 ± 6,5**	**79,7 ± 11,0**	**NS**

Maternal diastolic blood pressure

Maternal diastolic blood pressure is shown in Fig. 2. Repeated measures analysis was carried out on diastolic blood pressure using the repeated measurements taken at 5-minute intervals from 35 to 60 minutes. A significant treatment × time interaction was found ($P < 0,001$). This implies that the profiles of mean diastolic blood pressures over time do not lie parallel to one another. Differences at each point can therefore be tested. Univariate tests were carried out at each point and a significant fall in diastolic blood pressure was noted at 60 minutes (30 minutes after administration of the drug).

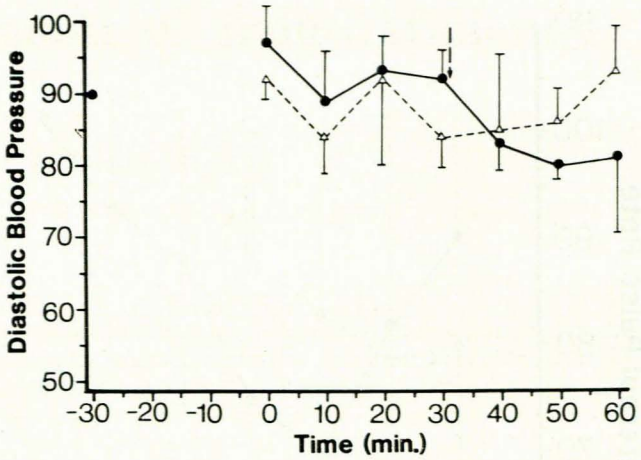

Fig. 2. Mean diastolic blood pressure (mmHg) plotted against time (min) for placebo (Δ) and nifedipine (•).

Maternal pulse rate

Maternal pulse rate is shown in Fig. 3. Repeated measurement analysis of variants showed a significant difference ($P < 0,001$) for treatment by time interaction.

Fetal heart rate

Fetal heart rate, as recorded with a cardiotocograph before and after administration of nifedipine or placebo, is shown in Table II. The Mann-Whitney non-parametric *U*-test showed no significant change in the fetal heart rate.

TABLE II. INDIVIDUAL MATERNAL AND FETAL MEASUREMENTS BEFORE AND AFTER ADMINISTRATION NIFEDIPINE 5 mg OR PLACEBO

	Patient	Mean diastolic blood pressure (mmHg)		Mean maternal pulse rate (/min)		Mean fetal heart rate (/min)		Gestational age (wks)	Mean Pourcelot ratio	
		Before	After	Before	After	Before	After		Before	After
Placebo	1	85	81	88	105	128	137	40	0,56	0,61
	2	97	85	68	85	145	145	34	0,68	0,67
	3	91	86	69	81	168	168	34	0,62	0,62
	4	85	78	101	124	150	155	36	0,57	0,61
	5	93	75	76	100	140	145	36	0,58	0,56
	6	109	101	100	110	140	155	33	0,60	0,44
	7	95	79	81	100	130	128	30	0,70	0,73
	8	98	81	63	66	128	148	37	0,61	0,57
	9	93	87	72	82	125	125	37	0,64	0,58
	10	88	84	79	83	160	155	34	0,55	0,62
Nifedipine	1	83	82	60	55	150	150	31	0,73	0,71
	2	92	90	110	110	145	145	38	0,52	0,47
	3	105	105	79	78	145	140	36	0,59	0,59
	4	105	107	76	74	160	160	32	0,58	0,60
	5	93	90	100	100	135	140	38	0,55	0,61
	6	87	91	60	59	125	125	31	0,70	0,69
	7	83	79	83	84	145	145	41	0,66	0,65
	8	83	78	80	79	145	155	33	0,64	0,64
	9	84	78	96	99	135	135	36	0,66	0,62

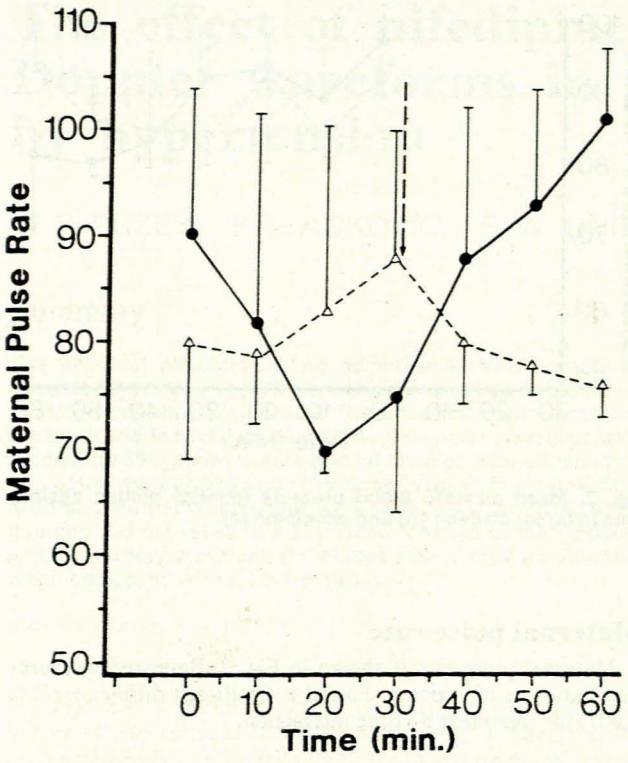

Fig. 3. Mean maternal pulse rate plotted against time (min) for placebo (Δ) and nifedipine (•).

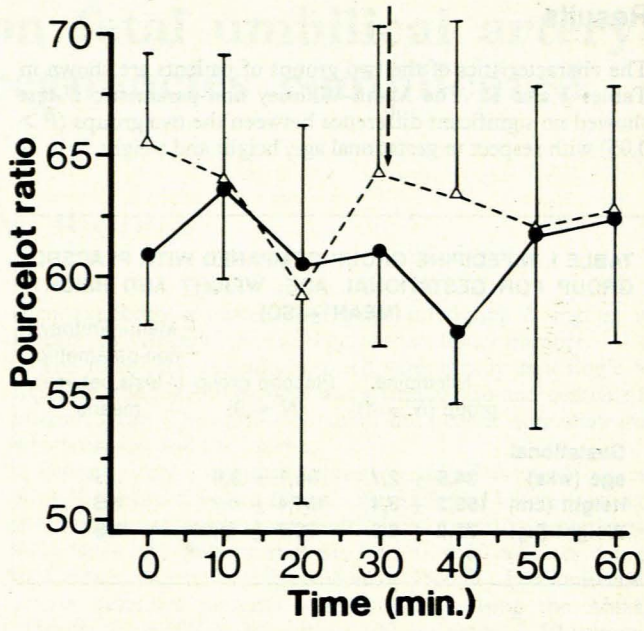

Fig. 4. Pourcelot ratio v. time (Δ = placebo; • = nifedipine).

Doppler waveform data/Pourcelot ratio

There were 5 missing values in this set of data due to fetal breathing movements. A missing value was replaced by either an interpolated value or the mean of the adjacent values. Fig. 4 gives the Pourcelot ratio v. time. Of note is that in both groups all the Pourcelot ratios were normal at the time of testing. No significant difference between the mean Pourcelot index in the two groups was detected ($P > 0,05$). In the nifedipine group the Pourcelot ratio measured at each time interval before and after administration of the drug showed no statistical change.

Side-effects

There were no maternal side-effects in either group. The continuous cardiotocograph recordings did not show any evidence of fetal distress.

Discussion

Nifedipine is a well-tolerated antihypertensive agent that is useful for both emergency and maintenance treatment. It is widely used in non-pregnant patients and is being prescribed in the treatment of hypertension of pregnancy with increasing frequency.

The use of any drug in the pregnant patient raises questions about its action on placental perfusion. The placenta is perfused by the fetal and maternal circulations independently and maternal ingestion of a drug may change either component. Study of the effects on the maternal blood supply of the placenta has indicated that there is no change in this aspect of placental perfusion.[7] Animal models have shown that nifedipine enters the fetal circulation in significant levels and increases cerebral blood flow altering fetal haemodynamics.[8] Further evidence for a possible effect of nifedipine on the fetal circulation has been studied *in vitro* and showed an interference in the contractile process in chorionic plate arteries and in the umbilical artery[9] leading to dilatation of these vessels. Guiseppe *et al.*[10] have studied the effect of nifedipine on the fetal umbilical artery waveform in normotensive patients and have indicated that there may be a beneficial response. As a result of the encouraging results in these trials we investigated the fetal responses to nifedipine in hypertensive pregnancies.

Our results indicate that nifedipine 5 mg, when given sublingually, does not cause any detrimental changes in the Doppler waveform analysis expressed as the Pourcelot ratio. This dose effected a drop in maternal diastolic blood pressure which was significant at 60 minutes (30 minutes after administration). It can be concluded that nifedipine 5 mg should have no adverse effects on the fetal circulation in the first 30 minutes after administration in fetuses with normal initial Doppler waveforms. There is a possibility that nifedipine in larger doses may produce a beneficial effect on the fetal placental blood flow, and we are at present investigating this.

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