Effects of Antihypertensive Drugs on Maternal and Fetal Hemodynamics and Uterine Blood Flow in Pregnant Goats — Comparison of Nicardipine and Labetalol

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ABSTRACT. This study was designed to compare the effects of nicardipine (0.02 mg/kg) and labetalol (0.5 mg/kg) on the uterine blood flow and fetal circulation after intravenous administration in unanesthetized, chronically instrumented pregnant goats. Significant decreases in maternal blood pressure and uterine blood flow were observed in both groups. The maternal heart rate increased significantly after the injection of nicardipine, whereas this change was not observed after the labetalol injection. The fetal heart rate, blood pressure and acid-base status did not change after the injection of either nicardipine or labetalol. These observations in pregnant goats suggest that both nicardipine and labetalol might be useful drugs for the treatment of acutely hypertensive crises in pregnant patients. — **KEY WORDS:** fetal hemodynamics, labetalol, nicardipine, uterine blood flow.

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An acute hypertensive crisis occurring in pregnancy must be treated promptly to avoid serious maternal and fetal complications, however, the effect of antihypertensive drugs on uterine arterial blood pressure (UBF) and the fetal cardiovascular system has not been fully clarified. UBF depends on maternal arterial blood pressure and is not maintained by autoregulation [8], and antihypertensive drugs might reduce UBF by decreasing the arterial blood pressure and the uterine perfusion pressure, which might also deteriorate fetal oxygenation. Non-invasive methods of examining changes in UBF are not available clinically, therefore, experiments using large animals like pregnant goats are valuable.

Hydralazine is one of the antihypertensive agents commonly used in obstetric practice. It is known to have a minimal effect on UBF, but might not be effective for 15–20 min following administration [7]. More effective, rapidly acting agents that do not cause significant changes in UBF, which produces adverse effects of the fetal condition, are desirable.

Nicardipine hydrochloride (NIC) is a calcium channel blocker with potent vasodilating and hypotensive properties [12], and labetalol is a combined alpha and beta antagonist [10]. There are, however, few reports on these drugs in the field of obstetrics, especially regarding the management of preeclamptic patients.

The present study was designed to compare the effects of nicardipine and labetalol on UBF and fetal circulation in chronically instrumented pregnant goats.

MATERIALS AND METHODS

The studies were performed on 8 pregnant Japanese Saanen goats, weighing from 35 to 50 kg, between 120 and 123 days (term=145 days) of gestation. These goats were cared for in accordance with the guidelines approved by the

Department of Veterinary Medicine of Kagoshima University for the care and use of animals. The animals were fasted for 24 hr before surgery. They were intubated, and anesthesia was maintained using O₂ (2 l/min), N₂O (2 l/min) and halothane (1.5%). Maternal femoral arterial and venous catheters (PE190, Intramedic, Clay Adams, Parsippany, New Jersey, U.S.A.) were inserted.

The gravid uterus of the pregnant goat was exposed, and the fetal head was exteriorized through a small hysterotomy incision. Polyethylene catheters (PE50, Intramedic, Clay Adams, Parsippany, New Jersey, U.S.A.) were inserted into the fetal carotid artery, jugular vein and trachea. Silver-silver chloride ECG electrodes were attached to the fetal chest wall. A catheter was placed in the amniotic cavity for the measurement of intrauterine pressure. The fetus was returned to the amniotic cavity and the uterine incision was closed. Finally, an electromagnetic blood flow probe (FH-020T, FC-040T, Nihon Kohden, Tokyo, Japan) was placed around the middle uterine artery and the peritoneal cavity was closed.

The animals were allowed to recover for 72 hr after the surgery. The maternal arterial blood pressure (MAP), maternal heart rate (MHR), and fetal arterial blood pressure (FAP) were measured continuously via catheters connected to previously calibrated, sterile pressure transducers (4-327-C, Bell & Howell, Los Angeles, California, U.S.A.). The ECG electrodes were connected to a variability polygraph (VPR-01, Atom, Tokyo, Japan) to obtain the fetal heart rate and variability. The flow probe was connected to an electromagnetic blood flow meter (MFV-1200, Nihon Kouden, Tokyo, Japan), which was then balanced. All the above information was recorded on a pensillograph (8K24-1-L, San-Ei, Tokyo, Japan). Arterial blood gases and pH were measured with a blood gas analyzer (165, Corning, Midfield, Massachusetts, U.S.A.) at 39°C immediately after each sampling.

During the course of the experiment, the animal was allowed to stand quietly in her cage. Following a 60-min control period, nicardipine (Yamanouchi, Tokyo, Japan) (0.02 mg/kg) or labetalol (Glaxo Nihon, Tokyo, Japan) (0.5 mg/kg) were injected over 2 min into the maternal femoral vein. The cardiovascular variables were measured at just before the drug injection, and at 5, 10, 20, 30, and 60 min after the drug injection.

If an animal was used more than once, there was a 2-day interval between one experiment and the next. None of the animals were used for more than 3 experiments.

The results are reported as the mean $\pm$ SEM. To compare

the effects of the two drugs on heart rate, arterial blood pressure, and UBF, data were expressed as % change from the control values. Data were analyzed by analysis of variance with repeated measures. When a significant F value ($p < 0.05$) was obtained, mean values were compared by a paired or unpaired t-test with Bonferroni's correction.

RESULTS

Six and five experiments were carried out in the nicardipine and labetalol groups, respectively. Figure 1 shows the responses of MHR, MAP, UBF, FHR, and FAP

Fig. 1. A recording of maternal heart rate (MHR), maternal arterial pressure (MAP), uterine blood flow (UBF), fetal heart rate (FHR), and fetal arterial pressure (FAP). An intravenous bolus of nicardipine (0.02 mg/kg) was given as indicated by the arrow.

Fig. 2. A recording of maternal heart rate (MHR), maternal arterial pressure (MAP), uterine blood flow (UBF), fetal heart rate (FHR), and fetal arterial pressure (FAP). An intravenous bolus of labetalol (0.5 mg/kg) was given as indicated by the arrow.

to a bolus injection of nicardipine (0.02 mg/kg). A fall in MAP and UBF accompanied by a rise in MHR was observed, but the FHR and FAP did not change. During the control period, mean MAP was 77.0 ± 2.6 mmHg and mean MHR was 101.0 ± 5.0 bpm. An intravenous nicardipine (0.02 mg/kg) injection caused a significant decrease in MAP and a significant increase in MHR of approximately 30-minutes' duration in these experiments. UBF decreased significantly at 5 min after the nicardipine injection, then returned to the control values within 30 min.

Figure 2 shows the responses of MHR, MAP, UBF, FHR,

and FAP to a bolus injection of labetalol (0.5 mg/kg). A fall in MAP and UBF was observed, but the FHR and FAP did not change. During the control period, mean MAP was 91.4 ± 4.2 mmHg and mean MHR was 122.6 ± 6.8 bpm. An intravenous labetalol (0.5 mg/kg) injection caused a significant decrease in MAP and in MHR. UBF also decreased significantly at 10 min after the labetalol injection, but returned to the control values within 30 min.

Figure 3 shows the percent change of maternal diastolic arterial blood pressure, UBF, and maternal heart rate from the control values. In both the nicardipine group and the

Fig. 3. Percent changes of diastolic arterial blood pressure (D-MAP), uterine blood flow (UBF), and maternal heart rate (MHR) from the control values. Each value is the mean $\pm$ SEM. "○" represents the nicardipine group and "□" represents the labetalol group. "*" and "**" respectively represent $p < 0.05$, and $p < 0.01$ in comparisons between the groups.

Table 1. Fetal heart rate, blood pressure, and fetal arterial blood gas status before and after drug administration

Nicardipine (n=6)		control	5 min	10 min	20 min	30 min	60 min
FHR (bpm)		187.3 $\pm$ 7.3	193.0 $\pm$ 4.5	190.8 $\pm$ 4.7	187.8 $\pm$ 3.8	182.2 $\pm$ 6.6	183.3 $\pm$ 4.7
S-FAP (mmHg)		57.8 $\pm$ 1.9	56.7 $\pm$ 1.2	59.2 $\pm$ 0.8	55.5 $\pm$ 1.7	50.7 $\pm$ 2.0	52.0 $\pm$ 1.4
M-FAP (mmHg)		40.3 $\pm$ 1.4	39.2 $\pm$ 0.9	40.3 $\pm$ 0.5	38.7 $\pm$ 0.7	39.8 $\pm$ 1.0	39.3 $\pm$ 0.4
D-FAP (mmHg)		31.5 $\pm$ 0.9	30.7 $\pm$ 1.0	31.2 $\pm$ 0.8	30.2 $\pm$ 0.7	30.8 $\pm$ 1.0	30.3 $\pm$ 0.8
pH		7.31 $\pm$ 0.01	7.34 $\pm$ 0.03	7.32 $\pm$ 0.03	7.34 $\pm$ 0.03	7.31 $\pm$ 0.04	7.32 $\pm$ 0.03
pCO ₂ (mmHg)		41.8 $\pm$ 0.8	38.8 $\pm$ 1.4	39.8 $\pm$ 1.3	43.5 $\pm$ 1.0	39.4 $\pm$ 1.3	38.3 $\pm$ 0.5
pO ₂ (mmHg)		17.1 $\pm$ 0.8	16.5 $\pm$ 0.9	17.1 $\pm$ 0.9	17.4 $\pm$ 1.1	17.3 $\pm$ 1.0	17.1 $\pm$ 0.8
Labetalol (n=5)		control	5 min	10 min	20 min	30 min	60 min
FHR (bpm)		171.4 $\pm$ 10.5	167.4 $\pm$ 14.3	171.6 $\pm$ 15.3	162.6 $\pm$ 13.1	158.4 $\pm$ 13.1	161.0 $\pm$ 14.6
S-FAP (mmHg)		59.6 $\pm$ 6.2	60.4 $\pm$ 6.1	58.6 $\pm$ 5.4	60.6 $\pm$ 5.9	61.4 $\pm$ 6.8	60.0 $\pm$ 5.6
M-FAP (mmHg)		47.6 $\pm$ 4.3	46.8 $\pm$ 4.0	45.6 $\pm$ 4.0	47.0 $\pm$ 4.1	47.4 $\pm$ 4.7	46.4 $\pm$ 4.3
D-FAP (mmHg)		39.8 $\pm$ 3.7	39.8 $\pm$ 3.2	40.0 $\pm$ 3.6	40.6 $\pm$ 3.7	41.4 $\pm$ 3.6	39.8 $\pm$ 4.0
pH		7.33 $\pm$ 0.01	7.31 $\pm$ 0.03	7.32 $\pm$ 0.05	7.32 $\pm$ 0.03	7.31 $\pm$ 0.01	7.35 $\pm$ 0.03
pCO ₂ (mmHg)		45.8 $\pm$ 2.0	38.0 $\pm$ 2.4	41.8 $\pm$ 1.6	42.8 $\pm$ 1.5	39.6 $\pm$ 1.8	38.7 $\pm$ 1.1
pO ₂ (mmHg)		18.4 $\pm$ 0.2	17.5 $\pm$ 0.2	18.1 $\pm$ 1.5	17.8 $\pm$ 1.8	15.3 $\pm$ 1.9	16.1 $\pm$ 0.7

S-FAP; systolic arterial blood pressure, M-FAP; mean arterial blood pressure, D-FAP; diastolic arterial blood pressure, Mean $\pm$ S.E.

labetalol group, the maximum decrease in diastolic blood pressure was recorded 5 min after treatment. The lowest diastolic blood pressure was similar between the two groups, however, the decrease in UBF was slightly greater in the labetalol group. The UBF at 10 min after treatment was significantly lower in the labetalol group than in the nicardipine group. The heart rate increased after nicardipine treatment, while it decreased after labetalol treatment. This inter-group difference continued to be seen throughout the observation period.

Table 1 shows changes in FHR, FAP, and acid-base status after maternally administered nicardipine and labetalol. Fetal tachycardia, bradycardia, fetal hypotension, fetal acidosis and fetal hypoxemia were not detected within the period of observation.

DISCUSSION

Antihypertensive drugs for use in pregnant women must satisfy the following requirements: (1) non-teratogenic; (2) do not compromise maternal cardiac function; (3) have no adverse effects on the fetal cardiovascular systems. Although various antihypertensive drugs have been given to pregnant women, the safety of all these drugs has not been completely established.

In the present study, both nicardipine and labetalol exhibited satisfactory hypotensive effects, however, the response of maternal heart rate to the two drugs differed markedly. Following nicardipine treatment, the heart rate showed a sudden rise of a seemingly reflex nature, which returned approximately to its control level 60 min later. On the other hand, the heart rate decreased only slightly after

labetalol treatment. This slight decrease in heart rate does not seem to adversely affect the heart, because labetalol dilates coronary blood vessels at the same time.

This study using pregnant goats revealed that the changes in UBF induced by nicardipine or labetalol at the dose levels used do not affect the fetal cardiovascular system, even though both drugs are water-soluble and cross the placenta [1, 6].

A possible explanation of why the fetal cardiovascular system was not affected in the current study is that the period of significant decrease in UBF was too mild and too short to have had any effect on these systems. Parisi *et al.* demonstrated negative effects of nicardipine on the fetuses of pregnant ewes: a significant increase in $p\text{CO}_2$ and a decrease in pH, with a trend toward decreased $p\text{O}_2$ 60 min after nicardipine administration (0.02 mg/kg/min, for 2 min) [9]. In their study, fetal placental blood flow decreased significantly (−27%), perhaps due to a more profound decrease in maternal blood pressure (−36%). Skillman *et al.* observed a decline in the fetal arterial $p\text{O}_2$ and O_2 contents, associated with reductions of 24% to 63% in UBF [13]. Although, in the study of Holbrook *et al.*, fetal heart rate and fetal arterial blood gas values did not change when 50 or 100 μg of nicardipine was directly administered to the fetus. They speculated that the previously reported fetal acidemia resulting from a maternal infusion of nicardipine might be due primarily to a decrease in the maternal uterine blood flow rather than to a direct fetal effect of the drug [2].

Another possible way to explain the unaffected fetal cardiovascular systems is that the decrease is compensated for by an increased cardiac output, which is related to a baroreceptor-mediated response by peripheral vasodilation [5]. Increased cardiac output following hydralazine administration is thought to be one of the reasons why hydralazine does not decrease UBF [11].

There are few studies that show the effects of labetalol on UBF in pregnant goats or sheep. Mandell *et al.* showed that labetalol may effectively decrease mean maternal blood pressure and improve UBF within 5 min of administration in the gravid ewe [4]. The fetal heart rate is apparently unaffected by labetalol treatment of hypertensive pregnant women, and Macpherson *et al.* concluded that labetalol did not cause a clinically important sympathetic blockade in the mature newborn infant [3]. Although the majority of newborns show no adverse clinical signs after exposure to labetalol, except for mild transient hypotension, they should be closely observed during the first 24–28 hr for bradycardia, hypotension, and other symptoms of α , β -blockade.

Very few clinical reports of hypertension during pregnancy have been published in the field of veterinary medicine. This might be either because hypertension seldom develops in pregnant animals because of anatomical,

physiological or nutritional differences from humans, or because the detection of hypertension in pregnant animals is difficult, due to the lack of established non-invasive methods of measuring animal blood pressures. If simple methods of measuring animal blood pressures are developed, more attention will be paid to hypertension during pregnancy in animals and to its treatment. Chronic experimental preparations using pregnant goats will provide a useful model for this kind of research.

In summary, we conclude that both nicardipine and labetalol may be an alternative to the currently used therapeutic agents for hypertension during pregnancy and further study is warranted.

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