The Effects of Medetomidine on Maternal and Fetal Cardiovascular and Pulmonary Function, Intrauterine Pressure and Uterine Blood Flow in Pregnant Goats

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Abstract: To investigate the effects of medetomidine on late pregnant goats, medetomidine induced changes in maternal or fetal circulation and acid-base balance, as well as changes in intrauterine pressure (IUP) and uterine blood flow (UBF), were studied. Intramuscular administration of medetomidine (40 μg/kg b.w.) decreased the heart rate (HR) and arterial blood pressure (ABP) of the mother, and the change in HR was significant statistically (p<0.05). In the fetus, HR and ABP showed a transient decrease and increase (p<0.05), respectively. A decrease in maternal arterial blood pH and oxygen partial pressure (PO2) and an increase in carbon dioxide partial pressure (PCO2) were recorded after the injection, but none was significant. In the fetus, arterial blood PO2 decreased significantly (p<0.05) after 5 min of administration, and a significant metabolic acidemia supported by a decrease in base excess was observed. Within 1 to 4 min after the administration of medetomidine, IUP began to rise and remained high for 10 to 14 min. Thereafter, the rise in IUP was frequent and periodical. After the injection, UBF significantly (p<0.05) decreased, and the fall in UBF was associated with a rise in IUP. The maternal and fetal serum medetomidine concentration increased remarkably after the injection of medetomidine into the mother. These observations in late pregnant goats suggested that medetomidine induced a decrease in maternal cardiac output, a decrease in UBF arising from the induction of uterine contractions, and transplacental medetomidine can have a suppressive effect on the fetus.

Key words: medetomidine, pregnant goat

Introduction

The chronic preparation model of catheterized pregnant small ruminants has provided substantial information on maternal and fetal physiology. During the preparatory operation, α2-adrenoceptor agonist has been used. Medetomidine, which was developed recently, is a highly selective α2-adrenoceptor agonist with
analgesic and sedative effects [21, 23]. Since medetomidine is widely used in equine and small animal practice for the following reasons: 1) the degree and the time of sedation can be easily controlled by the dosage, 2) a specific antagonist of atipamezole is established, and 3) anesthetic agents (i.e. injectable or inhalation general anesthetics) can be used in combination with it, it is expected to be used in experimental animals.

Suggested side-effects of medetomidine include a decrease in the heart rate and respiratory rate, A-V block, emetic effect [3, 22] and ptalism or tympany in ruminants [14, 15]. In particularly, uterine contraction, which is one of its side-effects in pregnant animals, is common to all α2-adrenoceptor agonists, and such studies as on an α2-adrenoceptor agonist of xylazine showed increased uterine activity and the absence of fetal breathing movements [6]. It was also reported that xylazine may cause abortion, because of its uterine contraction inducing action [2, 12]. Uterine contraction induced by medetomidine is suggested to be milder than that induced by other α2-adrenoceptor agonists in dogs and cattle [7, 18], but the effect on the fetal circulatory system was not determined synthetically. This study was conducted to evaluate the uterine stimulatory action and circulatory changes induced by medetomidine in the mother and fetus.

**Materials and Methods**

**Experimental animals:** The studies were carried out on twelve pregnant Japanese Saanen goats (28 to 45 kg, mean 32 ± 5.8 kg in body weight), between 125 and 135 days of gestation (term, 150 days). The animals were checked for clinical soundness by pre-operative examinations, including physical examination, clinical laboratory evaluation, radiography of the thorax and abdomen and echographic evaluation of the fetus. They were kept without food or water for 24 to 48 hr before the operation.

The surgical procedure was performed under rachianesthesia with mepivacaine hydrochloride (3 mg/ kg b.w.). An incision was made in the peritoneum, and a blood flow meter probe (type -FH020T, - FC040T, Nihon Kohden Co., Japan) with an inner diameter of 2-4 mm was mounted on the middle uterine artery. The gravid uterus was then exposed, and the fetal head was exteriorized through a small hysterotomy incision. 3.8 Fr (French scale) polyethylene catheters (PE90, Intramedic, Clay Adams, Parsippany, New Jersey, USA) were inserted into the fetal carotid artery and jugular vein. Electrocardiogram (ECG) electrodes were attached to the three subcutaneous points of the bilateral precordia and the dorsal cervix. A 4.7 Fr polyethylene catheter (PE160, Intramedic, Clay Adams, Parsippany, New Jersey, USA) was placed in the amniotic cavity to measure intracranial pressure (IUP). The fetus was returned to the amniotic cavity and the uterine and peritoneal incisions were closed. 4.7 Fr polyethylene catheters were inserted into the femoral artery and vein of the mother. The animals were allowed to recover for at least 48–72 hr after surgery.

**Measurements:** The maternal heart rate (HR), arterial blood pressure (ABP), IUP and fetal ABP were measured continuously via the catheters, which were connected to a variabilty polygraph (VPR-01, Atom Co., Tokyo, Japan) to monitor the fetal HR. The flow probe was connected to an electromagnetic blood flow meter (MFV-1200, Nihon Kohden Co., Tokyo, Japan), which was then balanced. All the above data were recorded on a pensillograph (8K24-1-L, San-ei Co., Tokyo, Japan). The maternal and fetal arterial blood pH, oxygen partial pressure (PO2) and increase in carbon dioxide partial pressure (PCO2) were measured by means of a blood gas analyzer (AVL995, AVL Scientific Co., U.S.A.), and corrected for body temperature. The base excess was derived by means of the standard formula. The serum medetomidine concentration was determined in the mother and fetus by a GC-MS method.

**Experimental protocol:** On the day of the experiment, the animal was allowed to sit quietly in her cage. Following the control period, medetomidine was administered intramuscularly at a dose of 40 μg/kg b.w., the same as by Mohammad et al. [14]. Maternal and fetal cardiovascular measurements were recorded and blood samples were obtained immediately before the medetomidine injection and at 5, 15, 30, 60 and 120 min after it. Based on the changes in IUP, a uterine contraction was defined as a rise in IUP sustained for more than 30 sec. The duration of uterine contraction
(DUC) per 10 min was calculated every 10 min up to 120 min after the injection of medetomidine.

Statistics: The measurements immediately before the medetomidine injection were used as control values. The UBF is expressed as the percentage change from the control value. All values are expressed as the mean ± SD. Statistical differences in the all parameters were analyzed by repeated measures ANOVA, and Scheffe's method was used for simultaneous multiple comparisons. Differences in P value less than 0.05 were considered to be statistically significant.

Results

Effects on maternal and fetal hemodynamics: Changes in HR and ABP in the mother and fetus after the administration of medetomidine are shown in Fig. 1. The maternal HR decreased significantly after the injection, and the value after 120 min was still significantly lower than the control value. The maternal ABP decreased and reached its lowest value after 60 min, but was not significant.

Intramuscular medetomidine caused a transient decrease and increase in the fetal HR and ABP, respectively, at 5 min after the injection, and the change in ABP was statistically significant. The variability in the fetal heart rate pattern disappeared after the injection of medetomidine. Throughout the experimental period, a rise in IUP tended to be accompanied by a fall in fetal HR and a rise in fetal ABP (Figs. 3-1 and 3-2).

Effects on maternal and fetal arterial blood pH and gases: Changes in arterial blood pH and gases in the mother and fetus after the administration of medetomidine are shown in Fig. 2. After the intramuscular medetomidine injection, the maternal arterial blood pH and PO₂ decreased and PCO₂ increased, but statistical differences were not detected in any parameters.

Medetomidine significantly decreased fetal arterial blood PO₂ and base excess, and the fetus showed signs of significant hypoxemia and metabolic acidemia.

Effects on intruterine pressure: A rise in IUP, which started between 1 and 4 min after the injection of medetomidine, continued for 10 to 14 min (Fig. 3-1). The mean DUC value (control values: 0 ± 0 min/10 min) rose significantly 10 and 20 min after the injection (values after 10 and 20 min: 7.5 ± 0.5 and 5.5 ± 1.9 min/10 min, respectively) (Fig. 4). These changes indicated the occurrence of persistent contractions in the uterus.

Following these persistent contractions, periodic contractions appeared frequently (Fig. 3-2), and the DUC values after 30 min of the injection tended to be higher than the control values (Fig. 4).

Effects on uterine arterial blood flow: UBF decreased significantly 5 and 15 min after the injection of medetomidine and tended to recover gradually, but was still lower than the control value after 120 min (60.5 ± 18.7%, not significant vs control value) (Fig. 4). Throughout the experimental period, a fall in UBF was associated with a rise in IUP (Figs. 3-1 and 3-2).

Serum medetomidine concentration: Intramuscular medetomidine increased the serum medetomidine concentrations in both the mother and fetus. The maternal value was the highest after 5 min (18.18 ± 8.39 ng/ml), and thereafter tended to decrease gradually (9.68 ± 4.55

![Fig. 1. Changes in maternal and fetal heart rate (HR) and arterial blood pressure (ABP) after administration of medetomidine (40 µg/kg b.w. i.m.) (mean ± SD, n=12). *: p<0.05 compared with the control values.](image-url)
Fig. 2. Changes in maternal and fetal arterial blood pH and gases after administration of medetomidine (40 μg/kg b.w. i.m.) (mean ± SD, n=12). *: p<0.05 compared with the control values.

Fig. 3-1. Responses of fetal heart rate (FHR), fetal arterial blood pressure (FABP), maternal heart rate (MHR), maternal arterial blood pressure (MABP), intrauterine pressure (IUP) and uterine arterial blood flow (UBF) immediately after administration of medetomidine (40 μg/kg b.w. i.m.).

Fig. 3-2. Responses of fetal heart rate (FHR), fetal arterial blood pressure (FABP), maternal heart rate (MHR), maternal arterial blood pressure (MABP), intrauterine pressure (IUP) and uterine arterial blood flow (UBF) 60 min after administration of medetomidine (40 μg/kg b.w. i.m.).
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ng/ml; after 15 min) (Fig. 5). In the fetus, the serum medetomidine concentration increased gradually after the injection, and peaked after 60 min (4.08 ± 1.06 ng/ml) (Fig. 5).

Discussion

This study aimed to evaluate the uterine stimulatory action and circulatory changes induced by medetomidine in the mother and fetus.

Noticeable decreases in HR and ABP shown in the mother after the administration of medetomidine suggested a decrease in cardiac output. A decrease in HR and an increase in ABP observed in the fetus were transient. These results were similar to those for xylazine studied previously [6, 20].

The medetomidine administration resulted in a decrease of maternal arterial blood pH and PO<sub>2</sub> and an increase of PCO<sub>2</sub>, and caused mild hypoxemia and respiratory acidemia. These results appeared to result from respiratory inhibition induced by medetomidine. In the fetus, arterial blood pH, PO<sub>2</sub>, and base excess decreased significantly. These findings suggested metabolic acidemia originating in hypoxemia in the fetus [13]. Although we reported that xylazine induced fetal metabolic acidemia [20], the metabolic acidemia developed by medetomidine (40 μg/kg b.w.) injection appeared to be more severe than that of xylazine (0.2 mg/kg b.w.).

IUP began to rise within 1 to 4 min after the injection of medetomidine and continued for 10 to 14 min after which frequent contractions occurred periodically. This persistent stimulatory effect has been demonstrated to be the direct action of α<sub>1</sub>-adrenoceptor agonists [19]. Jedruch et al. [7] reported that canine uterine electric activity decreased immediately after the administration of medetomidine at a dose of 20 μg/kg b.w., but increased persistently at doses of 40 and 60 μg/kg b.w.

In the horse, detomidine intramuscular injection at a practical dosage may not increase uterine electric activity [9]. In cattle, however, it was reported that detomidine induced a decrease in uterine activity at 20 μg/kg b.w. but an increase at 40 and 60 μg/kg b.w. [8] and that xylazine caused a rise in intrauterine pressure [10, 19]. Although, compared with these reports as for cattle, the time lag in the initiation and the duration of uterine activity was demonstrated in our present study, the tendency to a change observed in IUP was almost

Fig. 4. Changes in duration of uterine contraction (DUC) and in uterine blood flow (UBF) after administration of medetomidine (40 μg/kg b.w. i.m.) (mean ± SD, n=12). *: p<0.05 compared with the control values.

Fig. 5. Changes in maternal and fetal serum medetomidine concentration after administration of medetomidine (40 μg/kg b.w. i.m.) (mean ± SD, n=12).
the same. The time lag could be surmised to resulted from the difference in the subjects, the used drugs, the dosage or the administration route.

Subsequent to persistent uterine contractions, the frequency of periodic uterine contractions increased. This phenomenon was also observed in our previous study, using xylazine injection [20]. The mechanism underlying the periodic contractions caused by α2-adrenoceptor agonists has not been discussed in any of the earlier reports, but it was suggested that the excessive activation on α-adrenoceptor can enhance uterine contractility via destruction of the homeostasis between progesterone and α-adrenoceptor in the uterus [4, 17]. Medetomidine or the induced persistent uterine contraction could activate the mechanism bringing about the periodic contractions.

Medetomidine administration decreased UBF, and this change was negatively correlated with the change in IUP. These results agreed with those of our xylazine study, where we mentioned that the decrease in UBF could result more predominantly from the uterine contraction than the direct responses of xylazine via the α-receptors in the artery. This hypothesis is based on the results of Isla et al. [5]. They reported that in the uterine artery of late pregnant sheep the action mediated by α1-receptors is predominant, while the response mediated by α2-receptor is not marked. In the present study, the fact that medetomidine also has an uterine activating effect, which is enough to cause the decrease in UBF, was demonstrated.

In synchronization with the increase in IUP, UBF and fetal HR decreased, whereas fetal ABP increased. This indicates an deceleration pattern in fetal HR [16].

It has been suggested that α2-adrenoceptor agonists injected into the mother are able to be transmitted to the fetus via the placenta [11]. To our knowledge, however, no data have been presented on the transplacental transition of medetomidine to the fetus. In our pregnant goats, although the maternal serum medetomidine concentration reached its peak after 5 min of the injection and gradually decreased, the fetal serum medetomidine concentration increased gradually and maintained half as much as the maternal level. Lin et al. reported that the heart in fetal rats at 3 days before, immediately before, and at 3 days after birth, have an α2-adrenoceptor affinity 30, 20, and 15 times as great as in adults, respectively [11]. It therefore appeared that, compared to the mother, the action on the fetus via the α2-adrenoceptor can be greater regardless of the lower medetomidine level. Because we observed the disappearance of fetal heart rate variability supporting the neurological suppressive effect on the fetus in the present study, the changes in fetal hemodynamics and acid-base balance after the administration of medetomidine to the mother can be dependent on the transplacental medetomidine as well as secondary to the effects shown in the mother.

This study indicated that the administration of medetomidine to pregnant animals causes a decrease in cardiac output, an increase in uterine activity and a resultant decrease in uterine arterial blood flow in the mother. These effects of medetomidine were equivalent to those of xylazine [20]. Although these responses could be suppressed by the injection of a specific antagonist of atipamezole, medetomidine administration should be conducted carefully because of the undesirable maximum responses immediately after the injection.

References