Cardiopulmonary effects of xylazine and acepromazine in pregnant cows in late gestation

David S. Hodgson, DVM; Colin I. Dunlop, BVSc; Phillip L. Chapman, PhD; John A. Smith, DVM

Objective—To determine effects of sedation achieved by xylazine (XYL) or acepromazine (ACE) on cardiopulmonary function and uterine blood flow in cows in late gestation.

Animals—8 cows between 219 and 241 days of gestation.

Procedure—Doses of ACE (0.02 mg/kg) or XYL (0.04 mg/kg) were administered IV. Measurements were obtained to determine cardiopulmonary effects and oxygen delivery to the uterus.

Results—Heart rate was not significantly affected by administration of ACE, but it decreased markedly after administration of XYL. Uterine artery flow was decreased at all times by XYL and was always less than for ACE. Xylazine increased uterine vascular resistance through 30 minutes and caused reduced Pa_{O_2} and increased Pa_{CO_2} at all time periods. Acepromazine caused a 5% decrease in Pa_{O_2} only at 5 minutes. Xylazine reduced oxygen delivery by 59% at 5 minutes and 32% at 45 minutes. In contrast, ACE caused a nonsignificant reduction of oxygen delivery by 16% at 15 minutes and a return to baseline values by 45 minutes

Conclusions and Clinical Relevance—Xylazine markedly reduces flow and availability of oxygenated blood to the uterus, which may critically impair delivery of oxygen to the fetus at a stressful and important time of development or delivery. Acepromazine was associated with slight reductions of much shorter duration. When XYL is used to sedate pregnant cows, it could impose physiologic distress on the fetus and potentially increase fetal morbidity and mortality. When sedation of the dam is desirable, ACE could be an alternative to XYL. (*Am J Vet Res* 2002;63:1695–1699)

Dystocia is a common problem in heifers and cows and often requires intervention during parturition that may include fetal manipulation or cesarean section.[1,2] Survival of the calf usually depends on initiating these procedures while the fetus is still vigorous. Because these procedures are often performed under adverse conditions with minimal restraint, it is often desirable to sedate or tranquilize the dam. Unsedated cattle may become frightened and apprehensive, injuring themselves or the persons assisting them. Although the effects of stress on uterine perfusion and fetal well-being are unknown in cattle, uterine blood flow is reduced when ewes are exposed to painful or nonpainful stress.[3] Regardless of the type of obstetrical intervention, adequate oxygen delivery to the uterus is essential for the birth of a healthy calf. Reducing uterine blood flow or oxygen-carrying capacity of the blood is liable to harm the fetus and may increase fetal or neonatal mortality. Currently, **acepromazine (ACE)** and **xylazine (XYL)** are the 2 drugs most commonly used to sedate and tranquilize cattle. The effects of these drugs have been studied in nonpregnant cattle[a,b]; however, researchers have not yet determined how ACE and XYL affect oxygen delivery to the uterus in periparturient cattle.

The objective of the study reported here was to determine the manner by which these 2 drugs that are commonly used in managing dystocias might affect fetal viability. Our intent was to study how XYL and ACE affected uterine blood flow and oxygen-carrying capacity of blood flowing to the uterus in mature cows during the last 45 days of gestation.

Materials and Methods

Animals—Eight dairy cows (7 Holsteins, 1 Brown Swiss) that weighed (mean ± SD) 688 ± 57 kg and were 6.1 ± 1.8 years old were included in the study. All cows were between 219 and 241 days of gestation. Two weeks before the study began, the cows were moved to separate stalls in a veterinary teaching hospital barn and allowed to acclimate to the surroundings. A feeding regimen was maintained throughout the study. This study was approved by the Institutional Animal Care and Use Committee of Colorado State University.

Study design—Eight to 18 days prior to entry into the study, instruments were inserted in each cow in accordance with the procedure described by Dunlop et al.[4] Briefly, cows were held without feed for 48 hours and without water for 12 hours prior to surgery. Anesthesia was induced by IV administration of guaifenesin (75 mg/kg) and ketamine hydrochloride (1.75 mg/kg). Cows were intubated, and anesthesia was maintained by administration of halothane and oxygen delivered via a large-animal anesthetic machine. An incision was made in the lower aspect of the paralumbar fossa on the side corresponding to the gravid uterine horn. A segment of the uterine artery and vein supplying the gravid uterine horn was exposed. Polyethylene catheters were inserted into the uterine artery and vein. An ultrasonic transit-time flow transducer[c] was surgically implanted around the uterine artery at a

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From the Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences (Hodgson, Dunlop, Smith), and the College of Statistics (Chapman), Colorado State University, Fort Collins, CO 80523. Dr. Hodgson's present address is Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506. Dr. Dunlop's present address is 6 Ganora St, Gladesville, NSW 2111, Australia. Dr. Smith's present address is Fieldale Farms Co, PO Box 558, Baldwin, GA 30551.
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Address correspondence to Dr. Hodgson.

point proximal to the insertion site for the arterial catheter. Electronic signal of the flow transducer was monitored daily to ensure the flow transducer adequately encapsulated the artery. Encapsulation was considered complete when the amplitude of the electronic signal closely approximated the preimplantation value for the flow transducer. The study was initiated for each cow after it was determined that the flow transducer completely encapsulated the uterine artery. Number of days from implantation of the flow transducer until initiation of the study ranged from 8 to 18 days.

Measurement of variables—All baseline cardiopulmonary measurements and samples were obtained with the cows standing quietly in their stalls and restrained by a head gate. The same head gate was used for daily feeding, and restraint of cows in the head gate enabled investigators to monitor and care for the catheter and flow probe. In each cow, uterine arterial pressure was measured by use of a calibrated transducer[d] connected to a strip chart recorder.[e] Heart rate was determined from the resulting pressure recording. The pressure transducer was positioned at the level of the scapulohumeral joint. This position was assumed to be at the level of the outflow tract of the heart and was selected because it was not possible to determine the exact location of the catheter tip in the uterine artery after implantation. Pulsatile and mean uterine blood flows were electronically determined by use of an ultrasonic flow meter.[f] The resulting waveforms were recorded simultaneously. Uterine vascular resistance was estimated by dividing mean uterine arterial pressure by uterine blood flow.[5,6]

Respiratory frequency was determined by observation of thoracic and abdominal movements and then recorded. Uterine arterial and venous oxygen tensions, carbon dioxide tensions, and pH were measured by use of a calibrated blood gas analyzer.[g] Measurements were adjusted on the basis of each cow's rectal temperature, which was determined by use of a rectal thermistor probe.[h] Arterial oxygen content was derived by use of standard equations. Arterial PCV and serum protein concentration were measured. Uterine oxygen delivery was estimated by multiplying arterial oxygen content by uterine arterial flow.

Baseline cardiovascular and pulmonary responses of each cow were determined immediately prior to administration of xylazine hydrochloride[i] (0.04 mg/kg) or acepromazine maleate[j] (0.02 mg/kg) via the catheter in the uterine vein.[7] These dosages were selected on the basis that they are commonly used clinically and are expected to produce tranquilization and sedation without inducing recumbency. Measurements were obtained 5, 10, 15, 30, and 45 minutes after administration of XYL or ACE. We selected 45 minutes as an upper limit, because this usually exceeds the typical amount of time required for fetal extraction or delivery by cesarean section. Cows were randomly assigned to receive 1 of the drugs during the initial study period. At least 48 hours elapsed before the other drug was administered to the same cow, and the experiment was repeated.

Statistical analysis—All measurements were expressed as a percentage of the baseline values obtained immediately preceding treatment. A repeated-measures ANOVA with 2 factors (drug [XYL or ACE] and period [5, 10, 15, 30, or 45 minutes]) was performed. Also included in the model were random effects for animal, animal-by-period interaction, and animal-by-treatment interaction. Baseline periods were compared for each drug by use of a paired *t* test. Values of $P < 0.05$ were considered significant. If the drug-by-treatment interaction was significant, periods were compared separately for each drug among time periods by use of the least-significant difference method.

Results

Baseline values—Comparison of baseline values for each drug did not reveal significant differences, except for Pa_{O_2}, which had a mean of 85.0 mm Hg for XYL and a mean of 80.0 for ACE ($P = 0.015$). Because this was the only value that differed significantly between the drugs, we judged that this difference was likely to be spurious and reported the mean value for both drugs averaged over the 2 baseline periods (**Table 1**).

Cardiovascular response—After administration of ACE, heart rate was not significantly changed. In contrast, administration of XYL decreased heart rate, and administration of XYL always resulted in a slower heart rate than the administration of ACE (**Fig 1**). Uterine artery flow was markedly decreased after administration of XYL. Five minutes after administration, flow was reduced 56% from baseline values, but it gradually increased to only a 25% reduction at 45 minutes after administration. Administration of ACE did not significantly reduce flow, but flow was reduced 15 and 16% from baseline values 10 and 15 minutes after administration, respectively. Flow was always significantly higher after administration of ACE than after administration of XYL. The reduction in flow caused by administration of XYL was accompanied by an increase in uterine artery vascular resistance of 156 and 118% at 5 and 10 minutes after administration, respectively, and resistance remained significantly increased 30 minutes after administration. Administration of ACE did not significantly affect uterine artery vascular resistance, although we detected slight increases 10 and 15 minutes after administration. Resistance was significantly higher after administration of XYL throughout the 15-minute period after injection.

Pack cell volume was slightly reduced by 15 minutes after administration of either drug (**Fig 2**). Less reduction was detected 15 and 30 after administration of ACE than 15 and 30 minutes after administration of XYL. Administration of XYL caused reductions from baseline values of 7 and 6% at 30 and 45 minutes, respectively. Administration of ACE caused significant reductions of 2 to 5% in PCV from 15 through 45 minutes after injection. These reductions would have limited clinical importance. Administration of ACE or XYL did not significantly alter serum protein concentrations.

Pulmonary response—Respiratory rates were significantly reduced at all time points after administration of ACE and XYL (**Fig 3**). Reductions were greater 5 through 30 minutes after administration of XYL. Administration of XYL reduced respiratory rates by 38 to 57%, whereas administration of ACE reduced respiratory rates by 26 to 36%. Administration of XYL significantly reduced Pa_{O_2} at all times, and values for Pa_{O_2} after administration of XYL were always significantly less than the corresponding values after administration of ACE. Administration of ACE caused a reduction in Pa_{O_2} of only 6% at 5 minutes after injection. Administration of XYL also caused significantly higher

Table 1—Baseline values for cardiopulmonary variables obtained from 8 cows in late gestation

Variable	Mean ± SD*
Heart rate (beats/min)	66.6 ± 10.0
Mean uterine artery pressure (mm Hg)	84.0 ± 17.0
Uterine artery flow (L/min)	7.07 ± 2.70
Uterine vascular resistance (mm Hg/L/min)	13.5 ± 5.0
PCV (%)	31.4 ± 2.4
Serum protein concentration (g/dL)	7.5 ± 0.3
Respiratory frequency (breaths/min)	38.2 ± 0.2
Pa_{O_2} (mm Hg)	82.5 ± 4.0
Pv_{O_2} (mm Hg)	50.0 ± 2.0†
Pa_{CO_2} (mm Hg)	34.9 ± 3.0
pHa	7.424 ± 0.288
Arterial oxygen content (mL/dL)	13.20 ± 1.00
Venous arterial content (mL/dL)	10.52 ± 1.10†
O_2 delivery (mL/min)	926 ± 335
Rectal temperature (°C)	38.3 ± 0.2

*Data represent mean ± SD of the 2 baseline periods (1 baseline period preceding administration of each drug). †Represents data for only 6 cows.

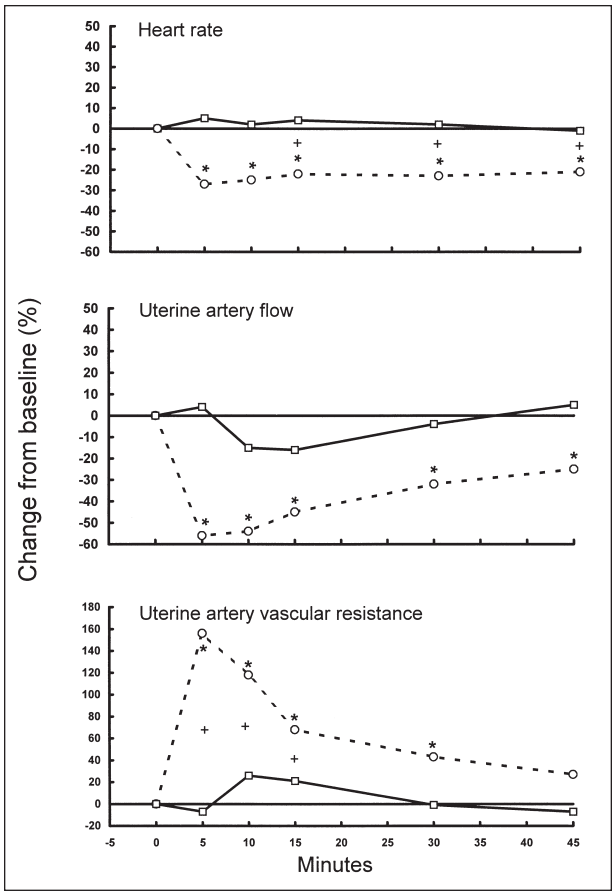

Figure 1—Percentage change in heart rate, uterine artery flow, and uterine artery vascular resistance after IV administration of xylazine (XYL; 0.04 mg/kg; open circles) or acepromazine (ACE; 0.02 mg/kg; open squares) in 8 cows in late gestation. Time 0 = Time of administration. *Value differs significantly ($P < 0.05$) from baseline value. +Value for XYL differs significantly ($P < 0.05$) from value for ACE.

Pa_{CO_2} at all time periods, compared with baseline values. The Pa_{CO_2} was not significantly altered by administration of ACE.

Concurrent with changes in uterine artery flow (Fig 2), administration of XYL significantly reduced arterial oxygen content and oxygen delivery at all time periods, compared with baseline values (**Fig 4**). Administration of ACE was not associated with significant reductions in arterial oxygen content or oxygen delivery. Uterine artery flow, arterial oxygen content, and oxygen delivery were always significantly lower after administration of XYL than after administration of ACE. Administration of ACE or XYL did not significantly affect venous oxygen content.

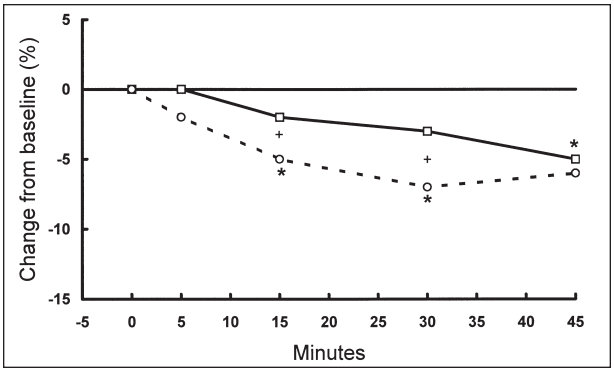

Figure 2—Percentage change in PCV after IV administration of XYL (0.04 mg/kg; open circles) or ACE (0.02 mg/kg; open squares) in 8 cows in late gestation. Time 0 = Time of administration. *See* Figure 1 for key.

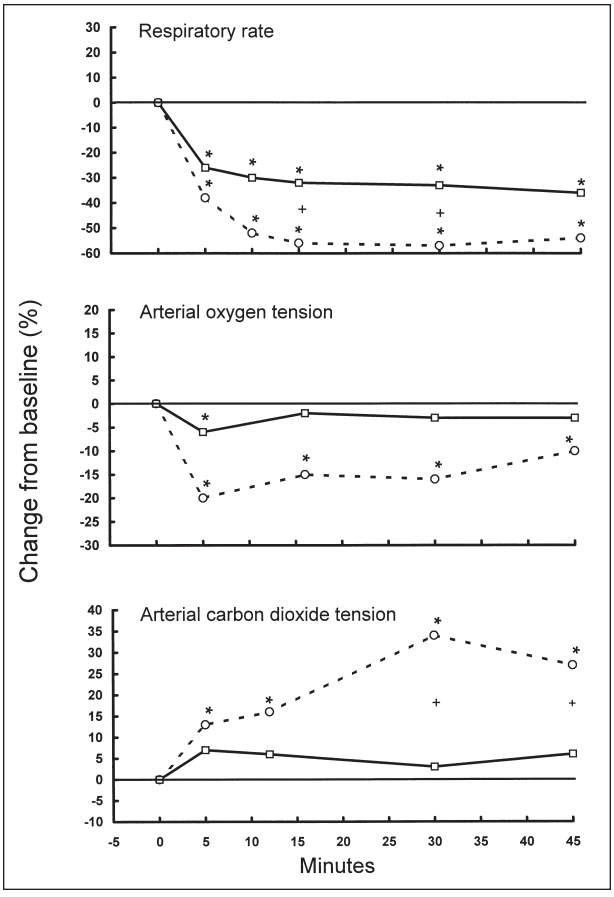

Figure 3—Percentage change in pulmonary responses after IV administration of XYL (0.04 mg/kg; open circles) or ACE (0.02 mg/kg; open squares) in 8 cows in late gestation. Time 0 = Time of administration. *See* Figure 1 for key.

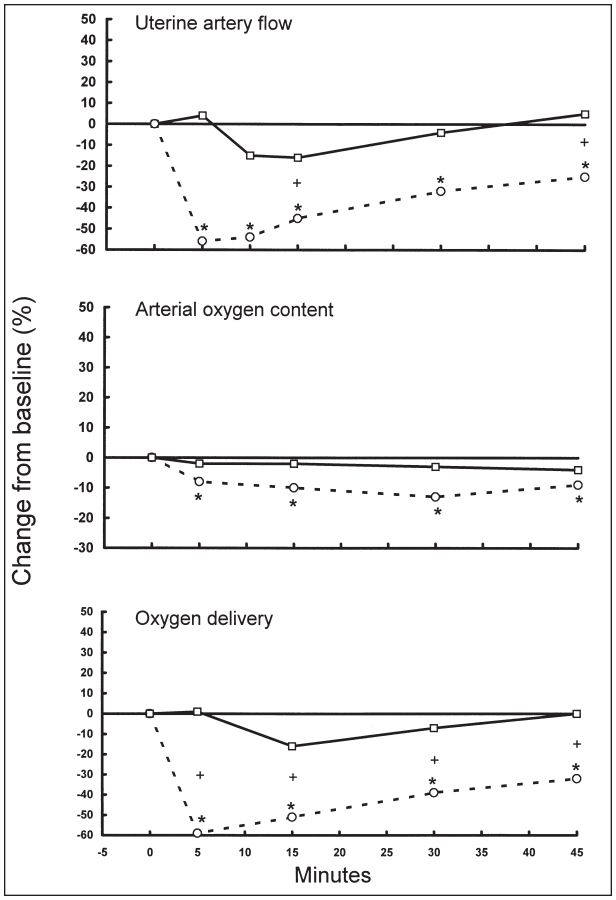

Figure 4—Percentage change in oxygen delivery and associated variables after IV administration of XYL (0.04 mg/kg; open circles) or ACE (0.02 mg/kg; open squares) in 8 cows in late gestation. Time 0 = Time of administration. *See* Figure 1 for key.

Discussion

Veterinarians who perform obstetrical procedures in cattle must be concerned with viability and oxygenation of the fetus during obstetrical manipulations, caesarean sections, and unassisted deliveries. Adequate blood flow that carries well-oxygenated blood to the fetus is needed to ensure the birth of a healthy calf. Because maternal stress and pain can reduce uterine blood flow in sheep,[3] veterinarians managing periparturient cattle may use sedatives, analgesics, or tranquilizers to reduce stress and pain. Although XYL produces more profound sedation than ACE, both drugs make cattle tractable and quiet. An advantage of XYL is the measure of analgesia provided, which is lacking with administration of ACE.

To our knowledge, cardiopulmonary effects of these drugs on uterine blood flow and oxygen delivery to the uterus in cattle and their subsequent effects on neonates have not been studied. Consequently, we investigated 2 tranquilizer-sedatives, ACE and XYL. Both drugs are commonly used in veterinary practice for sedating and calming periparturient cattle. None of the cows in our study became recumbent after administration of XYL or ACE at the clinically relevant dosages used. Administration of ACE produced obvious tranquilization in these cows within 10 minutes after IV injection. Administration of XYL caused more profound sedation, and effects were apparent within 5 minutes after IV administration. By assessing effects of these drugs on uterine blood flow and oxygenation of uterine blood, we determined that XYL may severely compromise oxygen delivery to the fetus, possibly resulting in fetal distress and lack of viability.

Analysis of results of our study revealed that administration of XYL reduced uterine artery flow and oxygen tension, markedly decreasing oxygen content of the arterial blood as well as the availability of blood delivery to the uterus. Consequently, oxygen availability to the fetus decreases. This would be especially detrimental if partial placental separation has occurred. On the other hand, when ACE was administered, the reduction in uterine artery blood flow was much smaller and of shorter duration. Also, administration of ACE did not significantly reduce oxygen tension, and arterial oxygen content was maintained. We calculated oxygen delivery by multiplying blood flow by oxygen content. Administration of ACE caused a nonsignificant reduction of oxygen delivery of only 16% at 15 minutes after injection. Oxygen delivery was not reduced further after that time.

The reduction in oxygen delivery of 59% caused by administration of XYL may be clinically important, especially if partial placental disruption has occurred. Severe and prolonged reduction in blood flow caused by administration of XYL can be attributed to several changes that are evident after its administration. There is a rapid and noticeable reduction in heart rate, which causes a concomitant reduction in blood flow when stroke volume cannot be increased. We observed that administration of XYL caused uterine artery vascular resistance to increase by 156% at 5 minutes after injection, and this increase persisted throughout the study. Because blood pressure did not increase significantly in these cows, less blood was pumped through the constricted artery. In contrast, administration of ACE did not significantly decrease heart rate nor significantly increase uterine vascular resistance. Thus, after administration of ACE, uterine artery blood flow was maintained near the presedation baseline value throughout our study.

Another reason for the decreased ability of arterial blood to deliver oxygen is a decrease in RBC mass per unit volume (ie, PCV). Administration of XYL reduced PCV significantly (7% reduction at 30 minutes and 6% reduction at 45 minutes). Administration of ACE reduced PCV by 3 and 5% at 30 and 45 minutes, respectively. A reduction in PCV may be attributed to various mechanisms. Red blood cells may be sequestered outside the circulating blood flow, or blood volume may increase as a result of extravascular fluid being drawn into the intravascular space. Because we did not detect a significant alteration in serum protein concentration, we believe that hemodilution is the least likely reason for the decrease in PCV, and cell sequestration is a more plausible explanation for this effect.

Adequacy of pulmonary ventilation is an important factor for oxygenation of maternal blood and, therefore, fetal blood. Whereas administration of XYL and ACE reduced respiratory frequency, the quantitative measure

of ventilation is $PaCO_2$. We found that administration of XYL increased $PaCO_2$ by 13 to 34%, which represents mild to moderate hypoventilation and resultant hypercapnia. Hypoventilation adversely affects oxygen content of RBC because of the fact it causes oxygen tension that is less than the physiologic reference range. Administration of ACE increased $PaCO_2$ by 3 to 6%, indicating mild hypoventilation. Hypoventilation after administration of XYL was more severe in our study and may have been clinically important; therefore, when delivering a fetus, clinicians should be especially aware that administration of XYL could have possible detrimental effects on ventilation.

The most important finding in the study reported here concerned the adequacy of oxygen delivery to the uterus. Direct measurement of arterial oxygen content used in the calculation of oxygen delivery would have been desirable; unfortunately, the instruments were not available for our use. Standard equations that were used should have provided a close approximation. A decrease in PaO_2 causes a reduction in arterial oxygen content. The result is a decrease in oxygen delivery when flow is not increased. A noticeable reduction in uterine artery flow was observed in our study when administration of XYL further decreased oxygen delivery, which could compromise fetal viability. Although administration of ACE reduced oxygen delivery by 16% at 15 minutes after injection, measurements obtained at other times were not significantly reduced. We are not aware of any studies that have examined fetal distress or morbidity or mortality during obstetrical manipulations in cattle. In humans, there is an abundance of reports and a heightened awareness of fetal status throughout obstetrical manipulations and delivery. Similar information for domestic animals would be of great interest to veterinarians.

When sedating pregnant cows, ACE may alleviate maternal stress and, thus, benefit the unborn fetus. Additional studies to directly examine fetal distress could provide useful guidelines for obstetrical management. A disadvantage for the use of ACE is that it does not provide analgesic effects. Clinicians should use local, regional, or epidural nerve blocks to eliminate or obtund pain when ACE is used for sedation.

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[a]Adetunji A, McDonell WN, Pascoe PJ. Cardiopulmonary effects of xylazine, acetylpromazine and chloral hydrate in supine cows (abstr), in *Proceedings*. 2nd Int Cong Vet Anesth, 1985;appendix.

[b]Warren RG, McDonell W, Adetunji A, et al. Cardiopulmonary effects of xylazine/halothane anesthesia in mature cows (abstr), in *Proceedings*. Am Coll Vet Anesthesiol Sci Meet, 1983;35–36.

[c]No. 24S, Transonic Systems Inc, Ithaca, NY.

[d]P23Db, Spectramed, Oxnard, Calif.

[e]Sanborne 2-channel physiograph, Hewlett-Packard Co, Waltham, Mass.

[f]T101D, Transonic Systems Inc, Ithaca, NY.

[g]Micro 13, Instrumentation Laboratory Inc, Lexington, Mass.

[h]YSI Model 43, Yellow Springs Instrument Co, Yellow Springs, Ohio.

[i]AnaSed Lloyd Laboratories, Division of Vetamix, Shenandoah, Iowa.

[j]Acepromazine maleate, TechAmerica, Fermenta Animal Health Co, Kansas City, Mo.

References

1. Corah LR. Relationship of nutrition and dystocia. *Agri-Practice* 1987;Feb:26–28.

2. Laster DB, Gregory KE. Factors influencing peri- and early postnatal calf mortality. *J Anim Sci* 1973;37:1092–1097.

3. Shnider SM, Wright RG, Levinson G, et al. Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. *Anesthesiology* 1979;50:524–527.

4. Dunlop CI, Hodgson DS, Smith JA, et al. Cardiopulmonary effects of positioning pregnant cows in dorsal recumbency during the third trimester. *Am J Vet Res* 1994;55:147–151.

5. Ladner C, Brinkman CP III, Weston P. Dynamics of uterine circulation in pregnant and non-pregnant sheep. *Am J Physiol* 1970;218:257–263.

6. Berman W Jr, Goodlin RC, Heymann Ma, et al. Relationship between pressure and flow in the umbilical and uterine circulations in sheep. *Circ Res* 1976:38:262–266.

7. Riebold TW, Geiser DR, Goble DO. Clinical techniques for food animal anesthesia. In: Riebold TW, Geiser DR, Goble DO, eds. *Large animal anesthesia*. Ames, Iowa: Iowa State University Press, 1995;41–142.