Sedative and cardiopulmonary effects of medetomidine hydrochloride and xylazine hydrochloride and their reversal with atipamezole hydrochloride in calves

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Objective—To assess the sedative and cardiopulmonary effects of medetomidine and xylazine and their reversal with atipamezole in calves.

Animals—25 calves.

Procedures—A 2-phase (7-day interval) study was performed. Sedative characteristics (phase I) and cardiopulmonary effects (phase II) of medetomidine hydrochloride and xylazine hydrochloride administration followed by atipamezole hydrochloride administration were evaluated. In both phases, calves were randomly allocated to receive 1 of 4 treatments IV: medetomidine (0.03 mg/kg) followed by atipamezole (0.1 mg/kg; n = 6), xylazine (0.3 mg/kg) followed by atipamezole (0.04 mg/kg; 7), medetomidine (0.03 mg/kg) followed by saline (0.9% NaCl; 10 mL), and xylazine (0.3 mg/kg) followed by saline solution (10 mL; 6). Atipamezole or saline solution was administered 20 minutes after the first injection. Cardiopulmonary variables were recorded at intervals for 35 minutes after medetomidine or xylazine administration.

Results—At the doses evaluated, xylazine and medetomidine induced a similar degree of sedation in calves; however, the duration of medetomidine-associated sedation was longer. Compared with pretreatment values, heart rate, cardiac index, and PaO\textsubscript{2} decreased, whereas central venous pressure, PaCO\textsubscript{2}, and pulmonary artery pressures increased with medetomidine or xylazine. Systemic arterial blood pressures and vascular resistance increased with medetomidine and decreased with xylazine. Atipamezole reversed the sedative and most of the cardiopulmonary effects of both drugs.


\(\alpha\)\textsubscript{2}-Adrenoceptor agonists including xylazine, detomidine, romifidine, and medetomidine are used to induce sedation, analgesia, anxiolysis, and muscle relaxation in a variety of species. Xylazine, the least selective of the \(\alpha\)\textsubscript{2}-adrenoceptor agonist drugs, was the first agent in this group to be licensed for use in veterinary medicine. In bovine veterinary practice, xylazine is routinely used to sedate calves that are undergoing procedures such as dehorning or castration; also, it is administered as a premedication agent to minimize stress associated with physical restraint and reduce the dose of drugs subsequently required to achieve anesthesia.\textsuperscript{1,2} Xylazine remains a popular drug among bovine practitioners because of its rapid onset and relatively short duration of action, analgesic properties, consistency and quality of sedation associated with both IM and IV routes of administration, and short tissue and milk withdrawal periods.

Received May 13, 2007.
Accepted August 1, 2007.

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Supported by the Foundation Alfonso Martin Escudero, which provided stipend funding for Dr. Eva Rioja during the study. Presented at the 2006 Annual Meeting of the American College of Veterinary Anesthesiologists, Chicago, October 2006.

The authors thank Gabrielle Monteith for assistance with the statistical analysis.

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ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CO</td>
<td>Cardiac output</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>RR</td>
<td>Respiratory rate</td>
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<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
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<td>MPAP</td>
<td>Mean pulmonary artery blood pressure</td>
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<td>CVP</td>
<td>Central venous pressure</td>
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<tr>
<td>CI</td>
<td>Cardiac index</td>
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<td>SVR</td>
<td>Systemic vascular resistance</td>
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<td>SI</td>
<td>Stroke index</td>
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<tr>
<td>P((A-a))O\textsubscript{2}</td>
<td>Alveolar-to-arterial oxygen tension difference</td>
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<td>Qs/Qt</td>
<td>Intrapulmonary shunt fraction</td>
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To date, medetomidine is the newest commercially available \(\alpha_2\)-adrenoceptor agonist drug. It is licensed for use in dogs and cats, although its use has been reported in a variety of other species including ruminants and horses.\(^6\,14\) Of the drugs of this class, medetomidine is the most potent, selective, and specific agonist (\(\alpha_2\), \(\alpha_1\) selectivity ratio, 1:620) in both peripheral and central nervous systems.\(^15\) and as such, it may offer some advantages over xylazine. Although the use of medetomidine for immobilization of free-ranging cattle\(^16\,17\) and wild ruminants\(^18\,20\) has been reported, clinical characteristics of the sedation induced by medetomidine, compared with those of xylazine-induced sedation, have not been extensively evaluated in domestic cattle to our knowledge.

Interestingly, there are dramatic differences in the clinical response and the dose requirements of \(\alpha_2\)-adrenoceptor agonists among species. Ruminants in general are particularly susceptible to the adverse effects of this group of drugs.\(^21\,22\) Although the overall cardiovascular effects of the \(\alpha_2\)-adrenoceptor agonists in ruminants and other species are similar, the magnitude of the decrease in oxygenation induced by this group of drugs is markedly greater in ruminants.\(^23\,28\) Other undesirable effects of the \(\alpha_2\)-adrenoceptor agonists that are particularly important in ruminants include the induction of reticulorumenal hypomotility with subsequent development of bloating and hemorrhagic depression.\(^25\)

Therefore, it is obviously desirable to have an efficacious reversal agent against the effects of \(\alpha_2\)-adrenoceptor agonists for use in these ruminant species.

Several \(\alpha_2\)-adrenoceptor antagonists including tolazoline, idazoxan, yohimbine, and atipamezole are currently available for use in veterinary medicine. Of these drugs, atipamezole is the most selective and potent antagonist of the central and peripheral \(\alpha_2\)-adrenergic receptors; it is marketed as the agent of choice for reversal of medetomidine-induced sedation in dogs and cats.\(^26\,27\) Although it may also be used for the reversal of other \(\alpha_2\)-adrenoceptor agonists such as xylazine or detomidine.\(^28\,29\)

Other advantages of atipamezole over the less-selective antagonists are the lack of activity at \(\beta\)-adrenergic, histaminergic, serotonergic, dopaminergic, \(\gamma\)aminobutyric acid, opioid, or benzodiazepine receptor sites.\(^20\) Atipamezole reverses the sedative, cardiovascular, gastrointestinal, and neuroendocrine effects of medetomidine in several animal species including laboratory rodents, dogs, cats, horses, and ruminants.\(^4,10-12,31-34\) It is also effective for the reversal of xylazine-induced sedation, bradycardia, and ruminal atony in calves.\(^28,29\) The pharmacokinetics of medetomidine and atipamezole in dairy calves and cows have been investigated.\(^7,8\) but the ability of atipamezole to reverse the cardiopulmonary effects of medetomidine or xylazine in calves has not been reported to our knowledge.

The purpose of the study reported here was to evaluate the sedative and cardiopulmonary effects of medetomidine and xylazine and their reversal with atipamezole in calves. The hypotheses were that, at the doses studied, medetomidine and xylazine would induce similar sedative effects and cardiopulmonary changes and that atipamezole would be able to completely reverse both the sedative and cardiopulmonary effects associated with either agent in dairy calves.

### Materials and Methods

The Animal Care Committee of the University of Guelph approved the procedures and the experimental design. Each calf used in the study was considered to be healthy on the basis of findings of a physical examination. Calves were housed individually during the study period. Food and water were not withheld prior to the study period. The study was performed in 2 phases with a minimum interval of 7 days between phases.

**Phase I**—Twenty-five male calves (mean ± SD age, 8.3 ± 4.9 days; weight, 47.0 ± 5.2 kg) were used in the first phase of the study. Prior to initiation of the experimental period, a catheter (20 gauge; 4.8 cm) was aseptically placed in a jugular vein of each calf. Calves were then randomly allocated to 1 of 4 groups: group M-A (n = 6) received medetomidine (0.03 mg/kg, IV) followed by atipamezole (0.1 mg/kg, IV), group X-A (7) received xylazine (0.3 mg/kg, IV) followed by atipamezole (0.04 mg/kg, IV), group M (6) received medetomidine (0.03 mg/kg, IV) followed by saline (0.9% NaCl) solution (10 mL, IV), and group X (6) received xylazine (0.3 mg/kg, IV) followed by saline solution (10 mL, IV). Atipamezole or saline solution was administered 20 minutes after administration of the \(\alpha_2\)-adrenoceptor agonist. All drugs were diluted to a final volume of 10 mL with saline solution and were administered IV via the previously placed jugular catheter (duration of injection, 10 seconds).

One investigator (ER) who was unaware of group allocations administered treatments to all calves and monitored sedation and recovery. Two minutes after administration of medetomidine or xylazine, the ease of placing each calf in lateral recumbency was recorded. Other data recorded included the interval from completion of medetomidine or xylazine injection until the calf achieved sternal recumbency initially (time interval 1) before being placed in lateral recumbency; intervals from completion of atipamezole or saline solution injection until the calf lifted its head (time interval 2), reestablished sternal recumbency (time interval 3), and attained a standing position (time interval 4); and, for groups M and X, interval from completion of medetomidine or xylazine injection until the calf was completely recovered from the induced sedation (able to stand without effort when stimulated by the observer and to walk normally without ataxia [evaluations were performed every 15 minutes], time interval 5). The number of attempts required for each calf to successfully achieve a standing position after the administration of atipamezole or saline solution was also recorded. In groups M-A and X-A, each calf was evaluated for signs of resedation every 15 minutes during a 90-minute period after the administration of atipamezole; resedation was considered to have developed if the calf remained recumbent or achieved a standing position only with evident effort when stimulated by the observer or if it walked with ataxia. After the completion of this phase of the study, the jugular catheter was removed.

**Statistical analysis of phase I data**—Commercial software was used for statistical analysis.\(^4\) For time intervals 1 through 5, a Levene test was used to test for normality and equality of variances among groups. For
time interval 1, data from medetomidine-treated groups (M-A and M) were pooled and xylazine-treated groups (X-A and X) were pooled; for specific variable, the difference was analyzed by use of a 1-way ANOVA. The differences in variables among time intervals 2 through 5 were analyzed by use of a 1-way ANOVA for group pairs as follows: M-A versus X-A, M versus X, M-A versus M, and X-A versus X. Post hoc comparisons were made by use of a Student t test for normally distributed variables and a Wilcoxon-Mann-Whitney test for nonnormally distributed variables. A value of P < 0.05 was considered significant. Data are reported as mean ± SD.

Phase II—Twenty-four male calves (mean ± SD age, 15 ± 5.6 days; weight, 49.3 ± 3.7 kg) were used for the second phase of the study. Twenty of these calves were the same as those used for the first phase of the study and remained in their allocated group, whereas 4 were additional calves that were randomly allocated to 1 of the 4 groups until all groups included 6 animals. The groups were otherwise the same as previously described for phase I. All calves entering phase II of the study were considered to be healthy on the basis of physical examination findings.

On the day of the experiment, anesthesia was induced in each calf by use of isoflurane in 100% oxygen delivered via a face mask and a rebreathing circle system attached to an anesthetic machine. Once a surgical plane of anesthesia was achieved, the trachea was intubated with an endotracheal tube (internal diameter, 10 to 12 mm). Anesthesia was maintained with isoflurane delivered in oxygen. An arterial catheter (20 gauge; 4.8 cm) was placed in an auricular artery for continuous monitoring of HR and systemic arterial blood pressures. The calf was placed in right lateral recumbency, and 2% lidocaine was injected SC over the left jugular vein. A 7-F Swan-Ganz pulmonary artery catheter was introduced through an 8.5-F introducer to obtain CO measurements via a thermodilution technique. Correct catheter placement was confirmed by observation of characteristic pressure-wave changes on a multiparameter monitor. The scapulohumeral joint was used as the zero reference point for both systemic arterial and pulmonary artery blood pressures.

Following instrumentation, each calf was transferred to a custom-designed sling mounted on the frame of a portable trolley to achieve a more physiologic and constant body position. While in the sling, the calf rested on its sternum and abdomen on a 13-cm-thick foam pad, with 1 limb protruding through each of 4 holes that had been cut in the foam pad. The sling maintained consistent head, neck, and thorax positions throughout the experiment. Once the calf was positioned in the sling, the administration of isoflurane was discontinued and it was allowed to recover from anesthesia.

One hour after recovery from anesthesia (extubation), baseline measurements including HR, RR, systolic and diastolic arterial blood pressures, MAP, systolic and diastolic pulmonary artery blood pressures, MPAP, CVP, core (pulmonary artery) body temperature, and CO were recorded. To measure CO, 10 mL of iced 3% dextrose solution was rapidly injected (3 seconds) into the right atrium via the proximal injection port of the Swan-Ganz catheter. Cardiac output was calculated as the mean of 3 values that were within 10% of each other. Immediately after baseline measurements, medetomidine or xylazine was administered (according to the group allocation) as performed in phase I. Atipamezole or saline solution was administered 20 minutes after the injection of α2-adrenoceptor agonist. As in phase 1, all treatments were given IV as a bolus during a 10-second period. One investigator (ER) who was unaware of group allocations administered treatments to all calves and recorded data. Cardiopulmonary variables were recorded at 5, 15, 25, and 35 minutes after medetomidine or xylazine administration in all groups. Arterial blood samples were also collected at the same time points and stored in ice for later pH and gas analysis and determination of PCV and total protein concentration. Blood gas analyses were always performed within 1 hour of sample collection. Additional values including CI, SVR, SI, and P(A–a)O2 were calculated by use of measured variables and standard formulas. After the completion of this phase of the study, all catheters were removed and the calves were returned to their individual stalls to be used for teaching purposes. Daily evaluations of the catheter insertion sites were made for 3 days after the study.

Statistical analysis of phase II data—A Shapiro-Wilk test was used to test data for normality. The effect of treatment group and time on the physiologic variables recorded over time was analyzed by use of an ANOVA for repeated measures. If the overall effect of the interaction between time and group was significant, post hoc comparisons with baseline values and comparisons among groups at the same time points were performed by use of a Dunnett test and a multivariate t analysis, respectively. A value of P < 0.05 was considered significant. Data are reported as mean ± SD.

Results

Phase I—Among the treatment groups, there were no significant differences in the weight or age of calves. All calves became profoundly sedated after administration of xylazine or medetomidine. Calves in groups M-A and M became sternaly recumbent (time interval 1) at 34 ± 14 seconds after medetomidine administration. For calves in groups X-A and X, time interval 1 was 28 ± 10 seconds after xylazine administration. These values were not significantly (P = 0.285) different. All calves, except 3 that received medetomidine and 1 that received xylazine, were easily placed in lateral recumbency 2 minutes after administration of the α2-adrenoceptor agonist. The remaining calves (n = 4) were easily placed in lateral recumbency 3 minutes after medetomidine or xylazine administration.

In general, all recorded time intervals were longer for calves in group M, compared with findings for calves in group X, and longer for calves in group M-A, compared with findings for calves in group X-A (Table 1). Calves in group M required significantly longer time to completely recover from sedation than did calves in group X. In addition, the time intervals recorded for calves that received saline solution (groups M and X) were significantly longer than those for calves that re-
ceived atipamezole (groups M-A and X-A). All calves stood at the first attempt after atipamezole administration in the M-A and X-A groups, whereas calves in groups M and X required 2.4 ± 1.5 and 2.8 ± 2.6 attempts to stand, respectively. During the 90-minute period of observation after administration of atipamezole (groups M-A and X-A), all calves except 1 in group X-A and 4 in group M-A were considered to be mildly resedated (reluctant to stand) at 60 minutes after atipamezole administration. Four calves in group M-A were considered to be mildly resedated (reluctant to stand or ataxic once standing) at 75 and 90 minutes after atipamezole administration. No adverse effects of the treatments were observed during the 7-day washout period between phases.

Phase II—Only 20 of the calves used in phase I were used for phase II; the remaining 4 calves necessary to provide 6 animals/group had not been used previously in the study. Four of the calves used in phase I were not included in phase II because they had been used during the 7-day washout period for teaching purposes. Among the treatment groups, there were no significant differences in the weight or age of calves. Cardiopulmonary variables were assessed before (baseline) and at intervals after administration of medetomidine or xylazine (Figures 1 and 2; Tables 2 and 3). Baseline values of any measured or calculated variable were not significantly different among groups.

Heart rate decreased significantly from baseline values at 5 and 15 minutes after medetomidine administration by 38% and 27%, respectively, and at 5 and 15 minutes after xylazine administration by 36% and 28%, respectively. In groups M-A and X-A, HR did not differ significantly from baseline values after atipamezole administration (at the 25- and 35-minute time points). However, HR values remained significantly lower than baseline by 28% and 26% in group M and by 29% and 31% in group X at 25 and 35 minutes, respectively.

Mean arterial blood pressure increased significantly from baseline values at 5 and 15 minutes after medetomidine administration by 24% and 13%, respectively, and returned to values similar to baseline at 25 minutes in both medetomidine groups (M-A and M). In the xylazine groups, MAP decreased significantly by 28% from baseline values at 15 minutes after administration, returning to values similar to baseline at 25 minutes after xylazine administration in group X-A but not in group X, where it remained significantly lower than baseline values by 34% and 32% at the 25- and 35-minute time points, respectively. Mean pulmonary artery blood pressure increased significantly from baseline values by 149% and 125% at 5 and 15 minutes after medetomidine administration, respectively, and by 91% and 26% at 5 and 15 minutes after xylazine administration, respectively. In groups M-A, X-A, and X, MPAP did not differ significantly from baseline values at the 25- and 35-minute time points. However, in group M, the value remained significantly higher than baseline by 90% and 83% at 25 and 35 minutes, respectively. Cardiac index decreased significantly from baseline values by 39% and 19% at 5 and 15 minutes after medetomidine administration, respectively, and by 18% at 5 minutes after xylazine administration. In groups M-A and M, CI did not differ significantly from baseline values at the 25- and 35-minute time points. In groups X-A and X, CI did not differ significantly from baseline values 15 minutes after xylazine administration.

In all groups, RR values were highly variable. There was a significant overall treatment and time effect on RR when these factors were studied separately, but a significant overall effect of the interaction between group and time was not identified. The PaO2 values decreased significantly from baseline values by 47% and 43% at 5 and 15 minutes after medetomidine administration, respectively, and by 49% and 29% at 5 and 15 minutes af-

Table 1—Mean ± SD duration (min) of time intervals 2 through 5 in dairy calves after IV administration of medetomidine (0.03 mg/kg) followed 20 minutes later by IV administration of atipamezole (0.1 mg/kg; group M-A; n = 6) or saline (0.9% NaCl solution (10 mL; group M; 6) or after IV administration of xylazine (0.3 mg/kg) followed 20 minutes later by IV administration of atipamezole (0.04 mg/kg; group X-A; 7) or saline solution (10 mL; group X; 6).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time interval</th>
<th>2</th>
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<th>5</th>
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<tr>
<td>M-A</td>
<td>1.55 ± 0.461†</td>
<td>1.67 ± 0.361†</td>
<td>4.24 ± 1.051†</td>
<td>NA</td>
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<tr>
<td>M</td>
<td>65.83 ± 38.86</td>
<td>66.25 ± 38.77</td>
<td>242.11 ± 108.67</td>
<td>420.8 ± 181.446</td>
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<tr>
<td>X-A</td>
<td>0.72 ± 0.361</td>
<td>0.83 ± 0.431</td>
<td>2.3 ± 1.468</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>19.38 ± 17.71</td>
<td>35.29 ± 37.34</td>
<td>128.18 ± 84.83</td>
<td>289.54 ± 73.86</td>
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*For each calf, time intervals recorded were as follows: 1 = time to achieve sternal recumbency after completion of medetomidine or xylazine injection; 2 = time to lifting of head after atipamezole or saline injection; 3 = time to restabilization of sternal recumbency after atipamezole or saline injection; 4 = time to standing after atipamezole or saline injection; and 5 = for groups M and X, time to complete recovery from sedation after medetomidine or xylazine injection (calf able to stand without effort when stimulated by the observer and to walk normally without ataxia [evaluations were performed every 15 minutes]). †At this time point, value for group M-A was significantly (P < 0.05) different from value for group M. ‡At this time point, value for group M-A was significantly (P < 0.05) different from value for group X-A. §At this time point, value for group M was significantly (P < 0.05) different from value for group X. NA = Not applicable.
ter xylazine administration, respectively. In groups M-A and X-A, PaO$_2$ did not differ significantly from baseline values at the 25- and 35-minute time points; however, it remained significantly lower than baseline at 25 and 35 minutes after medetomidine administration in group M and at 25 minutes after xylazine administration in group X. The PaCO$_2$ increased significantly from baseline values by 24% and 34% at 5 and 15 minutes after medetomidine administration, respectively, and by 26% and 27% at 5 and 15 minutes after xylazine administration, respectively. In groups M-A and X-A, PaCO$_2$ did not differ significantly from baseline values at 25 and 35 minutes; however, it remained significantly lower than baseline at these time points in groups M and X. The P(A-a)O$_2$ increased significantly, compared with baseline values, 5 and 15 minutes after medetomidine or xylazine administration in all groups and remained significantly increased at the 25- and 35-minute time
points, compared with the baseline value in group M. These increased PaO₂ values were also greater than the limit of 10.5 ± 2.3 mm Hg described for young animals breathing room air and with a physiologically normal Qs/Qt.

Arterial PCV remained within reference values (24% to 46%) in all groups at all time points. Total protein concentration was slightly less than the lower reference value (reference range, 5.9 to 7.7 g/L) in group X-A at all time points, but the differences from baseline value were not significant. The other 3 groups had total protein concentration values within the reference range at all time points, but the differences from baseline value were significant. We do not consider these differences to be clinically important. The selected atipamezole doses were considered equivalent in terms of reversal of sedation characteristics of the α₂-adrenoceptor agonist atipamezole. Atipamezole dose selection was based on the α₁/α₂ selectivity ratio of the α₂-adrenoceptor agonist and the period of time elapsed between the administrations of the α₂-adrenoceptor agonist and atipamezole. For antagonism of medetomidine in dogs, the recommended dose ratio of atipamezole to medetomidine is 5:1.

Intravenous administration of medetomidine (0.03 mg/kg) and xylazine (0.3 mg/kg) to calves resulted in a similar degree of sedation as assessed in the present study, although medetomidine-induced sedation lasted 2 hours longer than did xylazine-induced sedation. The sedative effects of medetomidine and xylazine were each reversed by a single dose of atipamezole (0.1 mg/kg and 0.04 mg/kg, respectively) when the reversal agent was given IV 20 minutes after α₂-adrenoceptor agonist administration. Those doses of atipamezole also reversed the respiratory effects and most of the cardiovascular effects of medetomidine and xylazine in the study calves.

In calves of the present study, the clinical effects associated with medetomidine and xylazine at the doses evaluated were characterized by a similar degree of deep sedation and ease of handling of the animals. The longer duration of the sedative effect of medetomidine was expected because its terminal half-life in cattle is longer than that of xylazine. The duration of the sedative effect of medetomidine administered IV at a dose of 0.04 mg/kg to dairy cows is as long as 7 hours, which is consistent with our results despite the dose and age differences between animals in both studies. In a previous study, dairy calves attained a standing position 95 minutes after IM administration of xylazine at doses ranging from 0.139 to 0.357 mg/kg. The time to standing after xylazine administration differs from that determined in the present study, likely because of the different dosage, route of administration, and age and breed of calves used in the 2 investigations.

Atipamezole (at the doses evaluated in the present study) fully and consistently reversed the sedative effects of each α₂-adrenoceptor agonist without causing excitation. After reversal with atipamezole, xylazine-treated calves lifted their heads and achieved a standing position in slightly less time than did medetomidine-treated calves; however, although these differences were significant, we do not consider them to be clinically important. The selected atipamezole doses were considered equivalent in terms of reversal of sedation characteristics of the 2 α₂-adrenoceptor agonists. Atipamezole dose selection was based on the α₁/α₂ selectivity ratio of the α₂-adrenoceptor agonist and the period of time elapsed between the administrations of the α₂-adrenoceptor agonist and atipamezole. For antagonism of medetomidine in dogs, the recommended dose ratio of atipamezole to medetomidine is 5:1. This recommended dose ratio has also been used in cattle and sheep to study the pharmacokinetics of medetomidine and atipamezole and used in sheep, goats, and free-ranging ruminants for sedation reversal. However, lower doses of atipamezole have also been successfully used for clinical reversal of the sedative effect of medetomidine in lambs (atipamezole-to-medetomidine ratio, 1:1).
and 2:1) and in free-ranging cattle (ratio, 2:1). For reversal of xylazine-induced sedation in calves, various atipamezole doses have been reported. Ratio doses of atipamezole (administered IV) to xylazine (administered IM) of 0.2:1 and 0.125:1 were effective and did not cause any undesirable effects or resedation in dairy calves. The atipamezole-to-xylazine and atipamezole-to-medetomidine ratios used in our study were 0.133:1 and 3.33:1, respectively, which are within the dose ranges described in the literature. This dose selection was also based on findings of a pilot study in which different doses of atipamezole in calves were evaluated.

After reversal of medetomidine-induced effects with atipamezole, resedation has been detected at 80 minutes after administration of the reversal agent in dairy calves and cows and at 1 to 2 hours or 3 to 4 hours after atipamezole administration IV or IM, respectively, in free-ranging cattle. In the present study, 2 of the calves were not considered to be resedated after medetomidine reversal, which may be attributable to the short period of observation (90 minutes) or to the criteria used to define resedation; we did not consider sternal recumbency a sign of resedation if the calves could stand effectively when stimulated and were bright, alert, and responsive. Both nonoccurrence and occurrence of resedation after reversal of xylazine with atipamezole in calves and free-ranging cattle have been reported. The fact that resedation was evident in only 1 calf after xylazine reversal could be a result of individual variations in either pharmacokinetics or pharmacodynamics of the drugs. Another less likely explanation is that resedation in the remaining 6 calves of that group was undetected because of the short period of observation, resedation criteria, or a combination of the 2 factors.

The cardiovascular effects of xylazine detected in the calves of the present study are in agreement with findings of previous investigations. In the first report of the hemodynamic effects of xylazine in calves, Campbell et al described immediate and prolonged decreases in HR, CO, systemic arterial blood pressures, and maximum rate of increase in left ventricular pressure after IM administration of 0.22 mg of xylazine/100 kg of body weight. After IV administration of 0.2 mg of xylazine/kg to calves, Doherty et al detected drug-associated sedative and cardiopulmonary effects, although they did not measure CO and pulmonary artery blood pressures. The hemodynamic effects detected in the present study were similar to those reported previ-
And were characterized by an immediate decrease in HR and a decrease in systemic arterial blood pressure 15 minutes after xylazine administration. In other species, different effects of xylazine on cardiovascular variables have been described; these differences appear to be dependent on both dose and route of administration.21-41

In adult cows, a decrease in HR and a variable effect on RR following medetomidine administration have been previously reported.2 With the exception of that study, no thorough evaluation of the cardiovascular and respiratory effects of medetomidine in bovines has been performed to our knowledge. In sheep, cardiovascular effects of medetomidine are characterized by decreases in HR, CO, and stroke volume; increases in MAP, SVR, and pulmonary vascular resistance; and no effect on CVP.11 In the present study, similar effects on HR, CI, and SVR were detected; however, effects on SI and CVP differed from the results in sheep. The increase in CVP in calves of the present study might reflect a combination of several effects induced by these agents: a decrease in HR and an increase in venous tone (both contributing to an increase in preload) and an increase in pulmonary arterial tone (and possibly pulmonary vascular resistance), resulting in an increase in right ventricular afterload. Compared with xylazine-sedated calves, pulmonary artery blood pressures were greater in medetomidine-sedated calves, and this might be one of the explanations for the comparatively greater increase in CVP induced by medetomidine.

The stroke volume is calculated as CO divided by HR; therefore, it can increase or decrease, depending on the degree and direction of change of the two variables from which it is determined. Also, a decrease in HR will increase the time for ventricular filling, thereby increasing the preload and, consequently, the stroke volume (Frank Starling law of the heart).44 In the present study, the increase in SI after xylazine or medetomidine administration could be attributable to a greater decrease in HR in proportion to the decrease in CI. A greater number of animals per group would have probably decreased the degree of variability in the SI results detected in our study.

Following administration of xylazine and medetomidine in some species, an initial increase in systemic arterial blood pressures following a return to baseline values or by a decrease from baseline values has been described.7,11,31,45 In the calves of the present study, increases in systemic arterial blood pressures following xylazine administration were not evident, but values

| Table 3—Mean ± SD values of arterial blood pH and HCO₃⁻ concentration, base excess, Pₐ-O₂, PCV, total protein concentration, and core (pulmonary artery) temperature in dairy calves after IV administration of medetomidine (0.03 mg/kg) followed 20 minutes later by IV administration of atipamezole (0.1 mg/kg; group M-A; n = 6) or saline solution (10 mL; group M; 6) or after IV administration of xylazine (0.3 mg/kg) followed 20 minutes later by IV administration of atipamezole (0.04 mg/kg; group X-A; 6) or saline solution (10 mL; group X; 6). Measurements were obtained before (baseline; 0 minutes) and at 5, 15, 25, and 35 minutes after medetomidine or xylazine administration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>0</th>
<th>5</th>
<th>15</th>
<th>25</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood pH</td>
<td>M+A</td>
<td>7.368 ± 0.02</td>
<td>7.307 ± 0.03*</td>
<td>7.259 ± 0.03*</td>
<td>7.397 ± 0.03*</td>
<td>7.388 ± 0.03*</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>7.393 ± 0.01</td>
<td>7.305 ± 0.03*</td>
<td>7.273 ± 0.04*</td>
<td>7.29 ± 0.04*</td>
<td>7.27 ± 0.07*</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>7.404 ± 0.04</td>
<td>7.317 ± 0.04*</td>
<td>7.308 ± 0.04*</td>
<td>7.426 ± 0.04*</td>
<td>7.416 ± 0.05*</td>
</tr>
<tr>
<td></td>
<td>X+A</td>
<td>7.393 ± 0.01</td>
<td>7.301 ± 0.01*</td>
<td>7.3 ± 0.03*</td>
<td>7.326 ± 0.02*</td>
<td>7.351 ± 0.03*</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>M+A</td>
<td>27 ± 2</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>27 ± 2</td>
<td>27 ± 2</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>27 ± 2</td>
<td>27 ± 2</td>
<td>26 ± 3</td>
<td>27 ± 3</td>
<td>27 ± 3</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>28 ± 3</td>
<td>30 ± 3</td>
<td>29 ± 3</td>
<td>29 ± 3</td>
<td>29 ± 4</td>
</tr>
<tr>
<td></td>
<td>X+A</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>Base excess</td>
<td>M+A</td>
<td>2.6 ± 2.1</td>
<td>1.1 ± 1.6*</td>
<td>-0.2 ± 1.8*</td>
<td>2.4 ± 1.8</td>
<td>2.4 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>2.9 ± 2.2</td>
<td>0.9 ± 2.1*</td>
<td>-0.6 ± 2.7*</td>
<td>-0.6 ± 2.6*</td>
<td>-0.3 ± 3.1*</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>4.7 ± 3.2</td>
<td>2.8 ± 3.3*</td>
<td>2.5 ± 3.4*</td>
<td>4.6 ± 3.1*</td>
<td>4.2 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>X+A</td>
<td>3.1 ± 1.8</td>
<td>1.4 ± 1.4*</td>
<td>1.2 ± 1.7*</td>
<td>1.7 ± 1.4*</td>
<td>2.4 ± 1.4</td>
</tr>
<tr>
<td>Pₐ-O₂ (mm Hg)</td>
<td>M+A</td>
<td>5 ± 10</td>
<td>35 ± 11*</td>
<td>25 ± 10*</td>
<td>11 ± 9</td>
<td>10 ± 7</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>2 ± 7</td>
<td>30 ± 7*</td>
<td>21 ± 4*</td>
<td>16 ± 5*</td>
<td>15 ± 8*</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>6 ± 5</td>
<td>33 ± 4*</td>
<td>15 ± 2*</td>
<td>14 ± 7</td>
<td>12 ± 6</td>
</tr>
<tr>
<td></td>
<td>X+A</td>
<td>8 ± 11</td>
<td>34 ± 10*</td>
<td>18 ± 6*</td>
<td>10 ± 6</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>M+A</td>
<td>30 ± 3</td>
<td>33 ± 4*</td>
<td>32 ± 4*</td>
<td>32 ± 4</td>
<td>31 ± 4</td>
</tr>
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<td></td>
<td>M</td>
<td>27 ± 7</td>
<td>29 ± 7*</td>
<td>28 ± 6</td>
<td>28 ± 7</td>
<td>28 ± 7</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>32 ± 5</td>
<td>35 ± 5</td>
<td>31 ± 4</td>
<td>31 ± 5</td>
<td>30 ± 5*</td>
</tr>
<tr>
<td></td>
<td>X+A</td>
<td>29 ± 4</td>
<td>28 ± 4</td>
<td>28 ± 4</td>
<td>28 ± 4</td>
<td>27 ± 4*</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>M+A</td>
<td>5.9 ± 0.5</td>
<td>6.1 ± 0.6*</td>
<td>6 ± 0.6*</td>
<td>5.9 ± 0.6</td>
<td>6 ± 0.5*</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>6.1 ± 0.5</td>
<td>6.3 ± 0.5*</td>
<td>6.3 ± 0.5</td>
<td>6.2 ± 0.5</td>
<td>6.3 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>5.6 ± 0.6</td>
<td>5.5 ± 0.6*</td>
<td>5.5 ± 0.5*</td>
<td>5.5 ± 0.5*</td>
<td>5.5 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>X+A</td>
<td>6.1 ± 0.3</td>
<td>6.2 ± 0.4</td>
<td>6.1 ± 0.3</td>
<td>6 ± 0.3</td>
<td>6 ± 0.3</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>M+A</td>
<td>38.7 ± 0.2</td>
<td>38.8 ± 0.2*</td>
<td>38.7 ± 0.2*</td>
<td>38 ± 0.2*†</td>
<td>38 ± 0.2*†</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>38.9 ± 0.3</td>
<td>39.2 ± 0.2*</td>
<td>39.2 ± 0.3*</td>
<td>39 ± 0.3*</td>
<td>38.8 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>38.6 ± 0.3</td>
<td>38.7 ± 0.3</td>
<td>38.7 ± 0.3</td>
<td>38.1 ± 0.3*†</td>
<td>38.2 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>X+A</td>
<td>38.9 ± 0.1</td>
<td>39 ± 0.2</td>
<td>39.6 ± 0.3</td>
<td>38.7 ± 0.3</td>
<td>38.5 ± 0.4*</td>
</tr>
</tbody>
</table>

*Within a group, value was significantly (P < 0.05) different from baseline for this variable.

See Table 1 for remainder of key.
were decreased, compared with baseline values, at 15 minutes after drug administration. These results are in agreement with those of a previous study\textsuperscript{11} in calves in which significant decreases in systemic arterial blood pressures were detected 10 minutes after IV administration of 0.2 mg of xylazine/kg. In other studies\textsuperscript{23,28} in sheep, administration of xylazine (0.15 mg/kg, IV) was not associated with significant changes in systemic arterial blood pressures. To our knowledge, there are no published studies in which the effects of medetomidine on systemic arterial blood pressures in calves were investigated. In sheep, systemic arterial blood pressures have been reported to increase or not change following administration of medetomidine at identical doses.\textsuperscript{5,23} The biphasic effect of increasing systemic arterial blood pressures at high doses and decreasing those blood pressures at low doses appears to be related to plasma concentrations of the $\alpha_2$-adrenoceptor agonists.\textsuperscript{67} The different effects of medetomidine and xylazine on systemic arterial blood pressures observed in our study as well as the interspecies differences are probably related to their different $\alpha_2:\alpha_1$ selectivity ratio or to the different distribution of $\alpha_2$-adrenoceptor subtypes within the body, although neither of these hypotheses has been proven.

The respiratory effects associated with medetomidine and xylazine administration in the present study are similar to results of previous studies in cattle and other ruminants. Respiratory changes in these species include decreases in arterial oxygen tension, with arterial and venous CO\textsubscript{2} tensions remaining within reference ranges or becoming increased, and increases in Qs/Qt.\textsuperscript{11,23,34-41,46,48} In sheep, the hypoxic effect induced by medetomidine or xylazine is quite severe; although several mechanisms may be involved, none have been confirmed nor any one of them thought to be solely responsible. One study\textsuperscript{23} in sheep revealed that administrations of the various $\alpha_2$-adrenoceptor agonists (when used at equipotent doses) result in a similar marked degree of hypoxemia and that the induced hypoxemia is not caused by hypoventilation or postural changes after drug administration. Results of previous studies\textsuperscript{26,40} have suggested that an increase in Qs/Qt, mediated by peripherally located $\alpha_2$-adrenoceptors, is 1 possible mechanism underlying $\alpha_2$-adrenoceptor agonist-induced hypoxemia. In the present study, the hypoxic effect induced by both $\alpha_2$-adrenoceptor agonists was attributable, at least in part, to an increase in Qs/Qt as indicated by the increased $P_{(\text{A}\text{a})}\text{O}_2$ (greater than reference values) at 5 and 15 minutes after their administration. In sheep, it appears that the increase in Qs/Qt associated with medetomidine administration and the subsequent oxygen-lowering effect is mainly a result of pulmonary dysfunction.\textsuperscript{52} Similar mechanisms might be involved in development of hypoxemia in boids, although these mechanisms have not been investigated.

Among the currently available $\alpha_2$-adrenoceptor antagonists that can be used to reverse the sedative and cardiopulmonary actions of $\alpha_2$-adrenoceptor agonists, atipamezole has the highest $\alpha_2:\alpha_1$ selectivity ratio.\textsuperscript{36} The other $\alpha_2$-adrenoceptor antagonists are poorly specific for those adrenoceptors; therefore, comparatively higher doses are needed to achieve the same degree of reversal as that achieved by use of atipamezole. Other $\alpha_2$-adrenoceptor antagonists may also have actions on other receptors (eg, $\beta$-adrenergic, histaminergic, serotonergic, dopaminergic, $\gamma$-aminobutyric acid, opioid, or benzodiazepine receptor sites\textsuperscript{29}), which increase the likelihood of adverse effects. Tolazoline and idazoxan reverse some of the cardiovascular effects associated with xylazine in cattle.\textsuperscript{8,41,51-53} Yohimbine appears to be less effective in reversing the bradycardic and sedative effects of $\alpha_2$-adrenoceptor agonists in ruminants, compared with tolazoline.\textsuperscript{5,24-50} In the present study, atipamezole successfully reversed the cardiovascular effects associated with xylazine or medetomidine in calves. Atipamezole is able to reverse the bradycardia induced by xylazine following IV\textsuperscript{49} or epidural\textsuperscript{26} administration in calves and buffaloes, respectively. In sheep and other nonruminant species, atipamezole can reverse the hemodynamic effects induced by medetomidine.\textsuperscript{11,52} To our knowledge, this is the first extensive investigation of the effects of atipamezole on hemodynamic changes induced by xylazine or medetomidine in calves.

Interestingly, the hypoxic effect that developed in both the medetomidine- and xylazine-treated calves was reversed by atipamezole administration in the present study. In lambs, atipamezole was able to reverse the sedative and cardiovascular effects, but not the decrease in arterial oxygen tension, induced by medetomidine.\textsuperscript{4} In adult sheep, atipamezole reverses medetomidine-induced hypoxemia to some extent but not completely.\textsuperscript{11} This difference in reversal effects could be a result of dosage differences among studies, although it is also possible that the mechanisms underlying $\alpha_2$-adrenoceptor agonist-induced hypoxemia are different or associated with less-severe effects in calves, compared with those in sheep.

Apparently, the effect of $\alpha_2$-adrenoceptor agonists on body temperature of ruminants is variable. Increases in body temperature following xylazine\textsuperscript{46} and medetomidine\textsuperscript{6} administration in cattle have been reported. However, medetomidine decreases body temperature in goats.\textsuperscript{28} In the calves of the present study, atipamezole administration was accompanied by a decrease in body temperature, which could be a result of the drug’s vaso-dilatory effect or the increase in ventilation associated with atipamezole. Packed cell volume was always within in physiologic range in all calves in the present study, and the differences encountered were not considered clinically important, although some were statistically significant. In some calves, total protein concentration was slightly less than the lower reference limit for adult cattle; however, this was not considered of clinical importance because total protein concentration is typically low at birth and increases gradually with age until the adult concentration is reached. Therefore, regardless of statistical significance, the differences in total protein concentration detected in the present study were not considered clinically relevant overall.

At the doses evaluated in the present study, atipamezole appeared to be an effective and safe agent for the reversal of the sedative and adverse cardiopulmonary effects of xylazine and medetomidine in healthy young dairy calves. From a sedative and cardiopulmo-
nary perspective, our findings do not suggest that medetomidine is a safer agent or that its use offers any advantage, compared with xylazine, in calves (at the doses that were administered). On the contrary, medetomidine-induced sedation and respiratory depression were of longer duration, which may be deleterious in some circumstances.

a. Domitor, Pfizer Canada Inc, Kirkland, QC, Canada.

b. Antisedan, Pfizer Canada Inc, Kirkland, QC, Canada.

c. Rompun, Bayer Inc, Toronto, ON, Canada.


f. Intro-Flex-Percutaneous sheath introducer kit, Edwards’ Lifesciences LLC, Irvine, Calif.

g. COM-2, Edwards’ Lifesciences LLC, Irvine, Calif.

h. Criticare Model 1100, Criticare System Inc, Waukesha, Wis.

i. ABL 700 Series Analyzer, Radiometer-Copenhagen, Copenhagen, Denmark.

References


