Comparison of the effects of xylazine bolus versus medetomidine constant rate infusion on the stress response, urine production, and anesthetic recovery characteristics in horses anesthetized with isoflurane

Catherine M. Creighton, DVM; Kip A. Lemke, DVM, MS, DACVA; Leigh A. Lamont, DVM, MS, DACVA; Barbara S. Horney, DVM, PhD, DACVP; Aimie J. Doyle, DVM, MS, DACVS

Objective—To compare the effect of xylazine bolus versus medetomidine constant rate infusion (MCRI) on serum cortisol and glucose concentrations, urine production, and anesthetic recovery characteristics in dorsally recumbent, spontaneously breathing, isoflurane-anesthetized horses.

Design—Prospective, randomized crossover study.

Animals—10 healthy Standardbreds.

Procedures—Horses were premedicated with xylazine or medetomidine IV. Anesthesia was induced with diazepam and ketamine and maintained with isoflurane for 150 minutes. For the xylazine treatment, end-tidal isoflurane concentration was maintained at 1.7% and xylazine (0.2 mg/kg [0.09 mg/lb]), IV) was administered as a bolus at the end of anesthesia. For the MCRI treatment, end-tidal isoflurane concentration was maintained at 1.4% and medetomidine (0.005 mg/kg/h [0.0023 mg/lb/h], IV) was infused throughout anesthesia. Serum cortisol and glucose concentrations were measured before, during, and after anesthesia. Urine specific gravity and volume were measured during anesthesia. Unassisted anesthetic recoveries were recorded by a digital video camera for later evaluation by 2 observers who were blinded to treatment.

Results—Serum cortisol concentration was lower and serum glucose concentration was higher with MCRI treatment, compared with xylazine treatment. Time to sternal recumbency was longer with MCRI treatment, but no difference was seen between treatments for times to extubation, first movement, or standing. Objective (mean attempt interval) and subjective (visual analog score) recovery scores were significantly better with MCRI treatment, compared with xylazine treatment.

Conclusions and Clinical Relevance—In isoflurane-anesthetized horses, premedication and administration of medetomidine as a constant rate infusion resulted in decreased serum cortisol concentration, increased serum glucose concentration, and superior anesthetic recovery characteristics, compared with conventional treatment with xylazine. (J Am Vet Med Assoc 2012;240:998–1002)
pofol in horses does not lead to an increase in serum cortisol concentrations even when surgical procedures are performed. The α₂-adrenergic receptor agonists are a routine component of IV anesthetic protocols, and this group of drugs decreases the stress response through their inhibition of sympathoadrenal output. The α₂-adrenergic receptor agonists also cause an increase in urine volume and a decrease in urine specific gravity, through interference with the action of vasopressin on the renal tubules and collecting ducts. Clinically, increased urine volume may impact the quality of anesthetic recovery as horses may attempt to stand too early in the recovery period due to discomfort from bladder distension.

The anesthetic recovery phase is a particularly dangerous time for horses, with approximately 25% of anesthesia-related death occurring from fractures during this period. Horses by nature are fight-or-flight creatures. This predisposes horses to attempts to flee during the excitement phase, which is invariably accompanied by ataxia and muscle weakness. As a result, many methods have been used in an attempt to reduce the incidence of catastrophic events during recovery. Assisted anesthetic recoveries are 1 approach and may include the use of head and tail ropes, soft padding, slings, air cushions, or pool recovery systems.

Sedation in the early recovery period has also been assessed as a method of improving the outcome of inhalant anesthesia by promoting a longer, smoother recovery. The α₂-adrenergic receptor agonists are the drugs most commonly used for this purpose. Historically, xylazine has been used for premedication prior to inhalation of anesthetics and is often given as a bolus injection prior to recovery.

Medetomidine, a more selective α₂-adrenergic receptor agonist, has recently been investigated in association with the use of inhalant anesthetics in horses. The short half-life of medetomidine in horses (51 minutes) and its selectivity and potency make it suitable for administration as a constant rate infusion to reduce the concentration of isoflurane required to maintain anesthesia in horses. The addition of MCRI to isoflurane anesthesia may result in improved cardiopulmonary stability, optimal analgesia and muscle relaxation, and improved anesthetic recoveries.

Anesthetic recoveries in horses are difficult to evaluate objectively. Multiple systems to score anesthetic recoveries have been proposed, and a universally accepted and validated recovery scoring system does not exist. Behavioral recovery scores that include timed endpoints as well as behavioral and strength assessments have been used in an attempt to standardize recovery scores by use of a comprehensive approach. Visual analog scores are simpler to use, involving a descriptive analog scale to subjectively evaluate overall recovery. Both of these systems can lead to disparate results between observers, depending on experience and interpretation. Mean attempt interval is a novel index for assessing anesthetic recoveries in horses and was used for the first time in the study reported here. This parameter was calculated by dividing the time between extubation and standing (in minutes) by the number of attempts to stand. Thus, the slow smooth anesthetic recoveries were distinguished from the fast scrambling recoveries or those recoveries that were prolonged because of weakness.

The purpose of the study reported here was to compare the effects of administration of a single IV bolus of xylazine at the end of anesthesia with that of MCRI administration throughout anesthesia on the stress response, urine production, and anesthetic recovery characteristics in horses. Without the confounding effects of surgery or the variability inherent in clinical trials. We hypothesized that MCRI would be associated with lower serum cortisol concentrations, higher serum glucose concentrations, increased urine production, and superior anesthetic recoveries, compared with xylazine bolus administration.

Materials and Methods

Animals—This study was approved by the university’s animal care committee and was conducted in compliance with published standards of animal care. Ten Standardbreds (5 mares, 4 geldings, and 1 stallion) were studied. Horses were owned by the Atlantic Veterinary College. The same horses were included simultaneously in a similar study in which different variables were measured in response to the same protocol. Power analysis done before the present study was begun revealed that 10 horses used in a crossover design had a power > 0.8 to detect a 10% change in biochemical values and recovery times and a 20% change in recovery scores. As previously reported, horses ranged in age from 3 to 7 years (mean ± SD, 3.8 ± 1.3 years) and weighed 400 to 560 kg (880 to 1,232 lb; mean ± SD, 450.3 ± 47.1 kg [990.7 ± 103.6 lb]). Horses were determined to be healthy; food but not water was withheld for 12 hours prior to anesthesia.

Experimental design—Horses were randomly assigned to 1 of 2 treatment protocols as already described; a statistical table of random digits was used. Briefly, horses were premedicated with either xylazine hydrochloride (0.7 mg/kg [0.32 mg/lb], IV) or medetomidine hydrochloride (0.007 mg/kg [0.0032 mg/lb], IV). Anesthesia was induced with diazepam (0.05 mg/kg [0.023 mg/lb], IV) and ketamine hydrochloride (2.5 mg/kg [1.14 mg/lb], IV). Horses were orotracheally intubated with a cuffed endotracheal tube and positioned in dorsal recumbency. Horses were connected to a large animal anesthetic circuit that provided isoflurane in oxygen. Connection to the breathing circuit was designated as time 0. Oxygen flow was 10 L/min for the first 10 minutes and 6 L/min thereafter for each treatment. The isoflurane vaporizer was set to maintain an end-tidal concentration of 1.7% (1.2 MAC isoflurane) in the xylazine treatment and 1.4% (1.0 MAC isoflurane) in the MCRI treatment. During the MCRI treatment, horses were given medetomidine at a rate of 0.005 mg/kg/h (0.0023 mg/lb/h), by use of a syringe pump. The infusion was started at 10 minutes after induction of anesthesia and stopped at the time isoflurane administration was discontinued. Horses were given an isotonic crystalloid solution (lactated Ringer’s solution, 5,000 mL) at a rate of 10 mL/kg/h (4.5 mL/lb/h) throughout each treatment. Horses that moved...
during the maintenance phase of anesthesia were given ketamine (0.5 mg/kg [0.23 mg/lb], IV). Anesthesia was maintained for 150 minutes. At the end of the xylazine treatment, horses were administered xylazine (0.2 mg/kg [0.09 mg/lb], IV) immediately before disconnection from the anesthesia machine. During recovery, oxygen was supplemented at 15 L/min by insufflation into the endotracheal tube until extubation, then nasally until horses rolled into sternal recumbency.

Data collection—Horses recovered from anesthesia in the same 3.4 × 3.6-m dimly lit recovery stall without assistance. Anesthetic recoveries were monitored by use of a high-resolution low-light camera41 and recorded digitally. Blood was drawn early in the morning of each treatment for analysis of serum glucose4 and cortisol6 concentrations. Data collection for all other parameters began at the time of connection to the breathing circuit (time 0). Blood was collected for measurement of serum glucose and cortisol concentrations at 30, 60, 90, and 150 minutes during anesthesia, 10 minutes after isoflurane administration was discontinued, and 30 minutes after the horses stood in the recovery stall.

A 20F, 54-inch-long urinary catheter was placed at the beginning of anesthesia, and the urinary bladder was emptied. Urine was collected in a 2,000-mL graduated cylinder for measurement of urine volume and specific gravity throughout anesthesia. Urine volume and specific gravity were measured at 30, 60, 90, and 150 minutes. The urinary catheter was removed immediately prior to transport to the recovery stall. Urine specific gravity was measured by use of a temperature-compensated handheld refractometer.

Anesthetic recoveries were continuously monitored and later evaluated by 2 observers, who were blinded to which treatment a horse received but were experienced in anesthetic recoveries in horses. Times to critical recovery events (extubation, first movement, sternal recumbency, and standing) were recorded during each recovery. One objective (MAI) and 2 subjective (VAS and BRS) recovery scoring systems were used. With MAI, a larger number indicates a slower recovery with fewer attempts to stand and defines a superior recovery. With VAS, a score of 0 represents the worst recovery possible and a score of 100 represents the best recovery possible.

Statistical analysis—Data analysis was performed by use of commercially available software packages. Serum cortisol and glucose concentrations and urine volume and specific gravity were analyzed by use of a 2-way repeated-measures ANOVA. When a significant treatment-time interaction was found, Holm–Sidak multiple comparison tests were used to compare differences between treatments over time. Significant P values for treatment-time interactions are reported. Early morning baseline serum cortisol and glucose values were compared by use of paired t tests. Recovery times, MAI, and VAS were also analyzed by use of paired t tests. The BRS results were analyzed by use of a Wilcoxon paired signed rank test. The mean of recovery scores from both observers was calculated before the data were analyzed. For all tests, values of P ≤ 0.05 were considered significant.

Results

Serum cortisol concentrations significantly increased over time with both treatments; however, this increase was less profound with MCRI treatment. Serum cortisol concentrations were significantly (P < 0.001) lower at 60, 90, and 150 minutes of anesthesia; 10 minutes after anesthesia; and 30 minutes after horses stood with MCRI treatment, compared with xylazine treatment (Table 1). The trial order also had a significant effect on baseline cortisol concentration. When data from both treatments were pooled, serum cortisol concentration was significantly (P = 0.009) lower at baseline in the second trial, compared with the first trial. Serum glucose concentrations were significantly (P = 0.009) higher with MCRI treatment at 150 minutes of anesthesia and 10 minutes after anesthesia, compared with xylazine treatment. The trial order did not have a significant effect on baseline serum glucose concentrations. Urine volume was higher and urine specific gravity was lower with MCRI treatment, compared with xylazine treatment, but there was considerable variation in values among horses, and this difference was not significant.

Mean time to sternal recumbency was significantly (P = 0.019) longer with MCRI treatment, compared

Table 1—Mean ± SD serum cortisol concentration, serum glucose concentration, urine volume, and urine specific gravity in 10 healthy adult isoflurane-anesthetized Standardbreds that received a single IV bolus of xylazine at the end of anesthesia or MCRI throughout anesthesia in a crossover study design.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Time after connection to breathing circuit (min)</th>
<th>10 minutes after disconnection</th>
<th>30 minutes after successfully standing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>XYL</td>
<td>123.4 ± 38.1</td>
<td>105.6 ± 22.4</td>
<td>129.2 ± 63.9</td>
<td>233.3 ± 72.9</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>MED</td>
<td>116.9 ± 20.7</td>
<td>95.6 ± 25.3</td>
<td>71.6 ± 11.3*</td>
<td>115.3 ± 46.7*</td>
</tr>
<tr>
<td></td>
<td>XYL</td>
<td>4.7 ± 0.3</td>
<td>6.5 ± 0.7</td>
<td>5.8 ± 0.6</td>
<td>5.6 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>4.8 ± 0.4</td>
<td>6.6 ± 1.2</td>
<td>6.4 ± 1.7</td>
<td>6.7 ± 1.9</td>
</tr>
<tr>
<td>Urine volume (mL)</td>
<td>XYL</td>
<td>106 ± 172</td>
<td>383 ± 426</td>
<td>97 ± 122</td>
<td>265 ± 293</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>303 ± 203</td>
<td>1,580 ± 564</td>
<td>1,370 ± 1,228</td>
<td>1,315 ± 1,024</td>
</tr>
<tr>
<td></td>
<td>ND</td>
<td>1,021 ± 0.013</td>
<td>1,018 ± 0.014</td>
<td>1,017 ± 0.011</td>
<td>1,020 ± 0.011</td>
</tr>
<tr>
<td></td>
<td>MED</td>
<td>1,015 ± 0.013</td>
<td>1,007 ± 0.003</td>
<td>1,006 ± 0.002</td>
<td>1,007 ± 0.003</td>
</tr>
</tbody>
</table>

*Significantly (P ≤ 0.05) different from xylazine treatment.

MED = Medetomidine. ND = Not determined. USG = Urine specific gravity. XYL = Xylazine.

Reference range for serum cortisol concentration was 70 to 180 nmol/L. Reference range for serum glucose concentration was 3.6 to 5.6 mmol/L.
with xylazine treatment (Table 2). Times to extubation, first movement, and standing and number of attempts to attain sternal recumbency and standing were not significantly different between treatments. Although both observers reported higher mean numbers of attempts to stand with xylazine treatment, compared with MCRI treatment, this difference was not significant. The MAI (P = 0.025) and VAS (P = 0.047) were significantly better with MCRI treatment, compared with xylazine treatment. Although the BRS was better with MCRI treatment, compared with xylazine treatment, this was not a significant finding. Recovery quality was better with MCRI treatment, compared with xylazine treatment, in 8 of 10, 7 of 10, and 6 of 10 horses when assessed by use of MAI, VAS, and BRS, respectively. The trial order did not have a significant effect on recovery quality.

Discussion

The \( \alpha_2 \)-adrenergic receptor agonists are known to inhibit the release of cortisol, a classic marker of the stress response. Although the mechanism of this effect is not completely understood, it may be due to a specific \( \alpha_2 \) receptor response, an indirect effect of the sedation and analgesia mediated by the \( \alpha_2 \) agonists, or other receptor responses. In the present study, serum cortisol concentrations were lower with MCRI treatment, compared with xylazine treatment, indicating that MCRI treatment blunted the stress response associated with inhalant anesthesia, compared with xylazine treatment. As the total cumulative dose of medetomidine was greater than that of xylazine, it is not surprising that the impact on cortisol was greater.

Baseline serum cortisol concentrations were greater for the first trial, compared with the second trial. This suggests that admission to the Veterinary Teaching Hospital was associated with a relevant stress response that diminished over the 10-day hospitalization period. Although all horses were admitted to the Veterinary Teaching Hospital for a minimum of 18 hours prior to their first trial, this finding indicates that 18 hours was not sufficient for complete acclimatization.

The increases in serum glucose concentrations observed with both xylazine and MCRI treatments were presumably a result of \( \alpha_2 \)-adrenoceptor–mediated inhibition of insulin release from pancreatic beta cells. Although xylazine has been shown to have a greater potential to increase serum glucose concentration, compared with medetomidine, after a single bolus injection, glucose concentrations were greater with MCRI treatment, compared with xylazine treatment in the present study. This suggests that the effect on serum glucose concentration is dose dependent, and the higher concentrations observed with MCRI treatment reflected the greater cumulative dose of drug given throughout anesthesia.

The \( \alpha_2 \)-adrenergic receptor agonists result in the production of large amounts of dilute urine, through their interference with the action of vasopressin in the renal collecting duct. Although not significant, urine volume was higher and urine specific gravity was lower with MCRI treatment, compared with xylazine treatment. Once again, this is not surprising in light of the greater cumulative dose of medetomidine, compared with xylazine.

The effects of MCRI and xylazine treatment on the duration of recovery can be evaluated by analyzing the times to critical endpoints (ie, extubation, first movement, sternal recumbency, and standing). Time to sternal recumbency was significantly longer with MCRI treatment, compared with xylazine treatment, despite the fact that horses were maintained at a lower end-tidal isoflurane concentration with MCRI treatment, compared with xylazine treatment (1.4% vs 1.7%). Although times to other critical endpoints (extubation, first movement, and standing) were not significantly different between treatments, they were longer with MCRI treatment.

Anesthetic recoveries in horses are difficult to evaluate because of the large number of factors involved and the subjective nature of the evaluations. For these reasons, a universally accepted and validated recovery scoring system does not currently exist. The authors have proposed a novel index for evaluating the quality of anesthetic recoveries in horses called MAI. This parameter defines an optimal recovery as one that is slow but characterized by scrambling or prolongation because of weakness. Time from extubation to standing was chosen because it represents a discrete time point, making the MAI more objective. Other time points such as time of disconnection from the breathing circuit may be more variable and therefore less standardized between horses.

Observer agreement was less variable when MAI was used to assess recovery quality, compared with when VAS and BRS were used. This may be due in part to the more objective nature of the MAI. In the present study, recovery quality was significantly better with MCRI treatment, compared with xylazine treatment, when assessed by use of MAI and VAS. However, the BRS was unable to detect
a significant difference. Horses subjected to > 1 recovery may undergo a learning phenomenon\textsuperscript{1,11,31}; this potential confounder was limited by the randomization of trial order. In the present study, trial order was not found to have a significant effect on the quality of recovery with any of the scoring systems used.

In horses anesthetized with isoflurane, premedication with medetomidine followed by administration of medetomidine as a constant rate infusion resulted in decreased serum cortisol concentrations and improved MAI and VAS recovery scores, compared with conventional treatment with xylazine. Further carefully controlled clinical trials are needed to fully evaluate the use of MCRI during inhalant anesthesia in horses undergoing surgery.

References