Article

Total intravenous anesthesia using a midazolam-ketamine-xylazine infusion in horses: 46 cases (2011–2014)

Turi K. Aarnes, Phillip Lerche, Richard M. Bednarski, John A.E. Hubbell

Abstract — This study evaluated use of midazolam, ketamine, and xylazine (MKX) for total intravenous (IV) anesthesia (TIVA) in horses. Medical records of 46 horses undergoing a clinical procedure using MKX for TIVA were reviewed. Age, breed, procedure, heart rate (HR), respiratory rate (RR), pre-anesthetic drugs, induction drugs, and total volume of MKX were recorded. Duration of anesthesia, time to standing, number of attempts to stand, and recovery score were also recorded. All horses were premedicated with an alpha-2 adrenoceptor agonist and anesthesia was induced with ketamine and midazolam. Duration of MKX infusion was 33 ± 14 min. Heart rate and RR decreased during the infusion of MKX. Time to endotracheal extubation was 19 ± 12 min. Horses stood at 33 ± 13 min. Median number of attempts to stand was 1. Maintenance of anesthesia of horses with MKX was useful for a variety of procedures and recovery from anesthesia was good.

Résumé — Anesthésie intraveineuse totale à l'aide d'une infusion de midazolam-kétamine-xylazine chez les chevaux : 46 cas (2011–2014). Cette étude a évalué l'usage du midazolam, de la kétamine et de la xylazine (MKX) pour l'anesthésie intraveineuse (IV) totale (AITT) chez les chevaux. Les dossiers médicaux de 46 chevaux subissant une intervention clinique à l'aide de MKX pour l'AITT ont été évalués. L'âge, la race, l'intervention, la fréquence cardiaque, la fréquence respiratoire, les médicaments pré-anesthésiques, les médicaments d'induction et le volume total de MKX ont été consignés. La durée de l'anesthésie, le délai pour se tenir debout, le nombre de tentatives pour se tenir debout et la note de rétablissement ont aussi été consignés. Tous les chevaux ont reçu une prémédication avec un agoniste alpha-2 adrénocepteur et l'anesthésie a été induite avec de la kétamine et du midazolam. La durée de l'infusion de MKX a été de 33 ± 14 min. La fréquence cardiaque et la fréquence respiratoire ont diminué durant l'infusion de MKX. Le délai jusqu'à l'extubation endotrachéale a été de 19 ± 12 min. Les chevaux se sont tenus debout à 33 ± 13 min. Le nombre médian de tentatives pour se tenir debout était de 1. Le maintien de l'anesthésie chez les chevaux avec MKX était utile pour une diversité d'interventions et le rétablissement de l'anesthésie a été bon.

(Traduit par Isabelle Vallières)

Can Vet J 2018;59:500–504

Introduction

Total intravenous anesthesia (TIVA) is a common anesthetic technique used in horses for procedures such as castration and laceration repair. The use of TIVA is facilitated using drugs that minimally depress cardiovascular and respiratory function because advanced equipment such as ventilators and blood pressure monitors, and additional technical support are often not available in field situations.

Solutions of guaifenesin, ketamine, and alpha-2 adrenoceptor agonists are commonly used for TIVA in the horse (1). Guaifenesin-ketamine-xylazine combinations have been studied extensively (2–5). This combination produces acceptable arterial blood pressure, mild to moderate hypoventilation, and good quality of recovery to standing (2). Guaifenesin solutions are no longer commercially available in the United States, Canada, Australia, and New Zealand. Reconstitution of guaifenesin powder into solution is time consuming and problems of precipitation out of solution have been reported (6). Additionally, guaifenesin solutions may induce hemolysis and thrombosis (6,7).

The benzodiazepine-midazolam may be a suitable alternative for guaifenesin for TIVA in the horse. Midazolam is water-soluble and when combined with ketamine, both drugs maintained potency for up to 97 h (8). Midazolam was investigated for use in combination with ketamine and xylazine for TIVA in Thoroughbred mares undergoing palmar digital nerve surgery (9). Midazolam was administered at a rate of 0.002 mg/kg

Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio 43210, USA.

Address all correspondence to Dr. Turi Aarnes; e-mail: Aarnes.1@osu.edu

Dr. Hubbell's current address is Rood and Riddle Equine Hospital, Lexington, Kentucky 40580, USA.

body weight (BW) per min, ketamine at a rate of 0.03 mg/kg BW per min, and xylazine at a rate of 0.016 mg/kg BW per min. Heart rate (HR), arterial blood pressures, cardiac output, and respiratory rate (RR) did not change from awake values during 70 min of anesthesia. Recovery from anesthesia was good with all horses standing on the first attempt (9). The combination appeared useful, but the study was limited in scope because of the homogenous population undergoing the same procedure. The objective of the present study was to describe the use of midazolam, ketamine, and xylazine (MKX) for maintenance of anesthesia in horses undergoing various clinical procedures and to evaluate its clinical suitability.

Materials and methods

Anesthetic records for all horses that underwent short-term anesthesia using MKX for TIVA between October 2011 and February 2014 were evaluated. Data obtained included age, breed weight, gender, procedure, pre-anesthetic drugs, anesthetic induction drugs, duration of infusion of MKX (defined as the start of infusion administration to cessation of infusion), duration of anesthesia (defined as time from administration of anesthetic induction drugs to cessation of MKX), and additional drugs administered. Heart rate and RR were recorded before anesthesia and at up to 5 time points (depending on duration of anesthesia): 10, 20, 30, 45, and 60 min. Time to standing (defined as the time from end of MKX infusion to standing), number of attempts to stand, and overall recovery score were also obtained.

Food, but not water, was withheld from horses for all planned procedures for approximately 6 h before anesthesia. All horses had a physical examination completed before anesthesia and an IV catheter was placed in a jugular vein using aseptic technique for drug administration. The horses' mouths were washed with water using a dosing syringe before induction of anesthesia.

Horses were sedated and all horses weighing more than 200 kg were positioned behind a hinged restraining door in a padded induction/recovery stall for induction of anesthesia. Horses weighing less than 200 kg were guided to recumbency by anesthesia personnel without the use of the hinged door during induction of anesthesia. Immediately after induction and achieving lateral recumbency, horses were orotracheally intubated with a cuffed endotracheal tube and the cuff was inflated at the discretion of the anesthetist. Supplemental oxygen *via* an oxygen demand valve or large animal anesthetic machine was administered at the discretion of the anesthetist. All horses breathed spontaneously. Horses were lifted by use of limb hobbles attached to a motorized hoist and positioned in the appropriate recumbency for the surgical procedure on a padded table.

Anesthesia was maintained using MKX, which was made by adding midazolam (West-Ward, Eatontown, New Jersey, USA), 25 mg, ketamine (VetaKet; Akorn, Decatur, Illinois, USA), 650 mg, and xylazine (Anased; Akorn), 325 mg, to a 500-mL bag of 0.9% saline. Administration began after the horse was positioned on the surgery table. The infusion was administered to effect using a 10 drop/mL drip set based on clinical signs of depth of anesthesia including palpebral reflex, corneal reflex, spontaneous blinking, lacrimation, muscle tension, horse movement, and change in respiratory rate, depth, or pattern. At the discretion of the anesthetist, additional drugs were administered as an IV bolus if the horse's depth of anesthesia indicated movement was imminent or if spontaneous movement occurred.

A base-apex electrocardiogram (ECG) was used to determine heart rhythm. Heart rate was determined by palpation of a peripheral artery. Respiratory rate was determined by observing chest excursions.

The total volume of the infusion that was administered was recorded. The infusion rate of each drug was calculated based on the total volume administered, the weight of the horse, and the duration of infusion. Any local anesthetic technique performed was noted.

At the end of the procedure, horses were transported from the padded table to the padded induction/recovery stall and lowered to the floor with a hobble and hoist system. Horses were positioned in lateral recumbency and the lights were dimmed. Head and tail ropes were used and sedation for recovery was administered at the discretion of the attending anesthetist. The orotracheal tube was removed after the horse attempted to swallow.

The time at which the horses stood and the number of attempts to stand were recorded. The quality of recovery was assessed by the attending anesthetist and scored on a 10-point scale:

1 = stands on first attempt with clean effort and no body sway or weight shifting;
2 = stands on first attempt with little to moderate effort and slight body sway or shifting;
3 = stands on first or second attempt with great effort and marked shifting once standing;
4 = 2 or 3 attempts to stand, with a strong effort on the last attempt and slight shifting once standing;
5 = 2 or 3 attempts to stand and marked instability once standing;
6 = several weak attempts to stand and marked instability once standing;
7 = several weak attempts to stand, horse resumes recumbency, and minor shifting is observed once standing;
8 = several weak attempts to stand, horse falls easily or resumes recumbency and incurs minor injury;
9 = several violent attempts to stand, horse falls or resumes recumbency and incurs minor injury; and
10 = several violent attempts to stand, horse resumes recumbency, and major injury is incurred by horse or personnel (9).

Heart rate and RR were recorded after standing while the horse remained in the recovery stall.

As many of the surgical procedures were less than 45 min in duration the 45- and 60-minute periods for HR and RR data were not analyzed. Descriptive statistics were calculated for each time period. Heart and respiratory rates were analyzed using Friedman test with a Conover's *post-hoc* test using MedCalc (MedCalc Statistical Software version 17.6, MedCalc Software, Ostend, Belgium). The 95% confidence intervals (CIs) for differences between medians were also calculated. Statistical significance was set at $P < 0.05$.

Table 1. Median (range) cardiopulmonary variables for 46 healthy horses that underwent total intravenous anesthesia (TIVA) maintained with a midazolam-ketamine-xylazine (MKX) infusion.

	Time[a]						
Variable	Baseline	10 min	20 min	30 min	45 min	60 min	After standing
HR (beats/min)	40 (24 to 60)	36 (24 to 56)[b]	34 (22 to 50)[b]	34 (24 to 58)[b]	35 (25 to 40)	36 (28 to 44)	40 (26 to 60)
RR (breaths/min)	20 (12 to 48)	8 (2 to 32)[b]	12 (4 to 32)[b]	12 (4 to 34)[b]	14 (4 to 40)	12 (4 to 20)	15 (8 to 26)[b]
Number of horses	46	46	43	37	13	5	31

[a] Baseline values were obtained the morning of the procedure. Remaining values were obtained from 10 to 60 min after the MKX infusion was started, and 10 min after horses stood during recovery. Times 45 and 60 min were not included in the analysis.
[b] Value is significantly different from baseline value.

Table 2. Anesthesia and recovery variables for 46 healthy horses that underwent total intravenous anesthesia (TIVA) maintained with a midazolam-ketamine-xylazine (MKX) infusion.

Variable	Mean ± SD	Median (range)
Midazolam infusion rate (mg/kg BW per minute)	0.002 ± 0.001	0.0017 (0.0003 to 0.0094)
Ketamine infusion rate (mg/kg BW per minute)	0.048 ± 0.033	0.042 (0.007 to 0.236)
Xylazine infusion rate (mg/kg BW per minute)	0.024 ± 0.016	0.021 (0.003 to 0.118)
Duration of infusion (min)	32 ± 14	30 (10 to 80)
Duration of anesthesia (min)	39 ± 15	36 (13 to 80)
Duration of procedure (min)	22 ± 14	19 (5 to 65)
Time to extubation (min)	18 ± 12	18 (0 to 38)
Time to standing (min)	33 ± 13	33 (12 to 59)
Number of attempts to stand	—	1 (1 to 5)
Recovery score	—	2 (1 to 8)

Timed recovery data are reported as mean ± SD and median (range) values as measured from the time that the MKX infusion was disconnected. Recovery score and number of attempts to stand are reported as median (range); quality of recovery was assessed in real time and scored on a 10-point scale in which 1 = stands on first attempt with clean effort and no body sway or weight shifting and 10 = several violent attempts to stand, horse resumes recumbency, and major injury is incurred by horse or personnel.

Results

Records from 46 horses were included in the study. Breeds included Thoroughbreds (n = 10), Quarter horses (n = 10), Warmbloods (n = 5), Arabians or Arabian crosses (n = 4), American Paint horses or Paint crosses (n = 4), Standardbreds (n = 2), American Saddlebreds (n = 2), Oldenburgs (n = 2), miniature horses (n = 2), Hanoverian (n = 1), Belgian (n = 1), Appaloosa (n = 1), and unknown breeds (n = 2). Age of the horses averaged 6.7 y with a range of 5 mo to 21 y of age. Weight of the horses averaged 430 kg with a range of 98 to 664 kg. Six mares, 15 geldings, and 25 stallions were included in the study. Horses were anesthetized by 5 different anesthetists.

Procedures performed included 19 castrations (1 with an abdominal testicle), 11 bone marrow aspirates, 5 wound/abscess debridement/joint flushing, 3 ophthalmic procedures [tissue plasminogen activation (TPA) factor injection or cyclosporine implants], 2 cast applications, 2 dental procedures, 1 umbilical hernia repair, 2 orthopedic procedures, and 1 myectomy.

All horses were premedicated with an alpha-2 adrenoceptor agonist. Xylazine was administered as the sole sedative in 23 horses at a mean ± SD dose of 0.92 ± 0.16 mg/kg BW, IV, and 1 horse received xylazine (1.05 mg/kg BW, IV) and butorphanol (Torbugesic, Zoetis, Kalamazoo, Michigan, USA), 0.02 mg/kg BW, IV. Romifidine (Sedivet; Boehringer Ingelheim Vetmedica, St. Joseph, Missouri, USA), 0.1 mg/kg BW, IV, was administered to 1 horse and detomidine (Dormosedan; Orion Corporation, Espoo, Finland), 0.01 mg/kg BW, IV, was given to 5 horses. Four horses were premedicated with detomidine, 0.01 ± 0.007 mg/kg BW, IV and 0.02 mg/kg BW, IM, and 1 of these horses also received butorphanol, 0.03 mg/kg BW, IV. Ten horses received acepromazine (Vedco, St. Joseph, Missouri, USA), 0.02 ± 0.003 mg/kg BW, IM, morphine (Hospira, Lake Forest, Illinois, USA), 0.06 ± 0.005 mg/kg BW, IM, and xylazine, 0.72 ± 0.16 mg/kg BW, IV, and 1 horse received xylazine, 0.35 mg/kg BW, IV and 0.7 mg/kg BW, IM and acepromazine, 0.02 mg/kg BW, IM. One horse received xylazine, 0.7 mg/kg BW, IV and detomidine, 0.004 mg/kg BW, IV.

Ketamine and midazolam in combination were administered to all horses for induction of anesthesia. The mean ± SD dose of ketamine was 2.15 ± 0.14 mg/kg BW and the mean dose of midazolam was 0.05 ± 0.01 mg/kg BW.

The mean ± SD of duration of MKX administration was 33 ± 14 min. The calculated mean ± SD infusion rates of midazolam, ketamine, and xylazine were 0.002 ± 0.001, 0.048 ± 0.033, and 0.024 ± 0.016 mg/kg BW per min, respectively. The mean ± SD total duration of anesthesia was 39 ± 15 min and duration of procedure was 22 ± 14 min.

Summary statistics for heart rate and respiratory rate for all horses and for all study periods are reported in Table 1. Median heart rates were lower at times 10, 20, and 30 min compared to baseline ($P < 0.05$) but were not significantly different between baseline and standing periods. Median respiratory rate was lower at times 10, 20, and 30 min and standing compared with baseline ($P < 0.05$).

Orotracheal intubation was not performed in 3 horses. Orotracheal intubation was performed in the other 43 horses, but in 2 of these horses the extubation time was not noted on the record. Time to extubation was 18 ± 12 min in 41 horses.

Fifteen horses (33%) received boluses of ketamine during the anesthetic period due to insufficient anesthetic depth: 2 (4%) of

these horses received ketamine immediately after induction and 2 horses (4%) received ketamine during transfer to the recovery stall. Six horses (13%) received additional xylazine: 2 of these horses due to insufficient depth of anesthesia, and 5 of these horses received xylazine as the horse was being transferred to the recovery stall for sedation going into recovery. One horse (2%) received additional xylazine immediately after anesthetic induction. Seven (15%) of the horses being castrated received intratesticular lidocaine (MWI, Boise, Idaho, USA) bilaterally before orchiectomy. Three of these 7 horses also received additional ketamine due to insufficient depth of anesthesia.

Horses stood at 33 ± 13 min after discontinuation of MKX infusion. The median number of attempts to stand was 1. Thirty-eight horses stood on the 1st attempt, 3 horses stood on the 2nd attempt, 4 horses stood on their 3rd attempt, and 1 horse stood on the 5th attempt. The median and mode recovery score was 2. The range of recovery scores was 1 to 8. One horse received a recovery score of 7 and 1 received a recovery score of 8. The horse that received the recovery score of 8 was a 4-year-old Arabian cross undergoing hoof debridement. This horse was extubated 3 min after the infusion ended, received ketamine (200 mg) and xylazine (150 mg) IV while moving to the recovery stall due to assessment of the attending anesthetist that the horse was "too light" (rapid nystagmus, extension of forelimbs). The recovery notes indicate 3 attempts to stand and subjectively described recovery as "very stormy" and the horse as "excitable." The horse with a recovery score of 7 was a 4-year-old Oldenburg anesthetized for a routine castration. The horse was extubated 17 min after cessation of the MKX infusion, made 4 weak attempts to stand and resumed recumbency until the last attempt to stand 5 min after extubation.

Discussion

Total IV anesthesia using MKX may be a useful alternative to combinations that included guaifenesin. The use of a skeletal muscle relaxant in combination with a dissociative anesthetic, and an alpha-2 adrenoceptor agonist has provided acceptable anesthesia for diagnostic and surgical procedures lasting less than 1 h and provided maintenance of arterial blood pressure, and acceptable respiratory and heart rates. Inclusion of a muscle relaxant reduces muscle rigidity associated with ketamine administration, and when given as a bolus extends the duration of ketamine-induced anesthesia (10). Guaifenesin-ketamine-xylazine (2), midazolam-ketamine-medetomidine (11), and guaifenesin-ketamine-romifidine (12) have been studied to provide TIVA in horses, and the combination of MKX was previously investigated for maintenance of anesthesia in horses undergoing digital nerve procedures (9). In the heterogenous group of horses studied here, the infusion of MKX provided suitable anesthesia for various surgical procedures.

The duration of TIVA in horses is often limited to an approximately 1-hour duration due to concerns regarding drug accumulation (13). In this study, the mean duration of infusion administration was 33 ± 14 min and the approximate mean infusion rate of midazolam was 0.002 ± 0.001 mg/kg BW per min, of ketamine was 0.048 ± 0.033 mg/kg BW per min, and xylazine was 0.024 ± 0.016 mg/kg BW per min. The infusion rate was adjusted during the procedure by the anesthetist based on clinical evaluation of depth of anesthesia. These rates are similar to those initially investigated by Hubbell et al (9) who administered these drugs for 70 min with no adverse effects noted. Midazolam in the present study was administered during anesthetic induction at a dose of 0.05 ± 0.01 mg/kg BW and subsequently as an infusion. Pharmacokinetics of midazolam after a single bolus of 0.05 mg/kg BW resulted in no change in cardiorespiratory parameters, but did result in swaying and weakness in standing horses (14). Pharmacokinetics of midazolam administered as an infusion in horses have not been studied.

Different sedation protocols were used in the horses in this study and could have affected the results. Some horses received opioids (morphine or butorphanol) and/or acepromazine for sedation and pain, in addition to an alpha-2 agonist for premedication. Opioids may cause excitement in horses and acepromazine has been associated with ataxia (15). While these may have impacted recovery scores, the inclusion of these drugs is common in clinical anesthesia of horses.

Heart rate and RR remained within physiologic ranges for the duration of the infusion; however, heart rate and RR decreased during the infusion compared with baseline. Previous investigation of MKX resulted in no change in HR, cardiac output, or arterial blood pressures (9). Invasive blood pressure was not monitored in these clinical patients.

Total intravenous anesthesia techniques are frequently used in field situations due to the ease of administration and lower cost, and because anesthesia can be provided without the transportation of anesthetic machines and oxygen sources. Producing anesthesia without the ability to ventilate the horse or supplement FiO_2 has the potential to compromise ventilation and decrease oxygenation, although reports on the use of TIVA suggest that the levels of hypoventilation and/or hypoxemia associated with TIVA do not compromise patient safety (13). Care should be taken in applying these results to the equine population as a whole because respiratory function was assessed as normal prior to anesthesia in the horses used in most of these studies. Horses with pre-existing disease would probably benefit from supplementation of FiO_2 and perhaps mechanical ventilation, although there is scant evidence that the presence of arterial oxygen tensions in anesthetized horses below values seen in standing horses affects mortality. The largest study on equine mortality associated with anesthesia reports that TIVA is associated with lower mortality rates than inhalant anesthesia (16).

Oxygenation and adequacy of ventilation were not evaluated in these clinical patients through arterial blood gas monitoring; however, in the previous study of MKX, partial pressures of arterial carbon dioxide ($PaCO_2$) did not change from baseline values, indicating adequate ventilation while partial pressures of arterial oxygen (PaO_2) decreased from baseline values during 60 min of anesthesia (9). Intubation was performed, but these horses breathed room air spontaneously (9). This is consistent with another study evaluating midazolam-ketamine-romifidine, in which normocarbia but impaired oxygenation occurred (17). Additionally, a previous study of xylazine, ketamine, and guaifenesin administration reported moderate hypoventilation

with normal oxygenation in ponies spontaneously breathing oxygen (4). Although healthy anesthetized horses appear to be amazingly tolerant of variations in ventilation and oxygenation, consideration should be given to intubating and ventilating, or providing oxygen supplementation to horses anesthetized with MKX whenever possible.

The retrospective study design is a limitation of the study. Some data were incomplete, such as time of extubation. The lack of standardized anesthetic protocol is a confounding factor for determination of the effects of MKX on depth of anesthesia and recovery.

The clinical nature of the patients included in the study demonstrate that midazolam-ketamine-xylazine infusion is a suitable technique for anesthetizing horses for surgical and diagnostic procedures of 1 hour or less duration while utilizing a variety of pre-anesthetic protocols.

Acknowledgments

The authors thank RVTs Carl O'Brien, Amanda Cardenas, and Devin Heilman; Drs. Nicole Karrasch, Michael Lovasz, and Kerrie Lewis for technical assistance, and Dr. John Bonagura for statistical assistance. CVJ

References

1. Hubbell JAE, Saville WJA, Bednarski RM. The use of sedatives, analgesic, and anaesthetic drugs in the horse: An electronic survey of members of the American Association of Equine Practitioners (AAEP). Equine Vet J 2010;42:487–493.
2. Young LE, Bartram DH, Diamond MJ, Gregg AS, Jones RS. Clinical evaluation of an infusion of xylazine, guaifenesin and ketamine for maintenance of anaesthesia in horses. Equine Vet J 1993;25:115–119.
3. Muir WW, Skarda RT, Sheehan W. Evaluation of xylazine, guaifenesin, and ketamine hydrochloride for restraint in horses. Am J Vet Res 1978; 39:1274–1278.
4. Greene SA, Thurman JC, Tranquilli, Benson GJ. Cardiopulmonary effects of continuous intravenous infusion of guaifenesin, ketamine, and xylazine in ponies. Am J Vet Res 1986;47:2364–2367.
5. McCarty JE, Trim CM, Ferguson D. Prolongation of anesthesia with xylazine, ketamine, and guaifenesin in horses: 64 cases (1986–1989). J Am Vet Med Assoc 1990;197:1646–1650.
6. Pang DSJ. Anesthetic and analgesic adjunctive drugs. In: Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA, eds. Veterinary Anesthesia and Analgesia: Lumb & Jones. 5th ed. Ames, Iowa: Blackwell Publishing, 2015:244–259.
7. Grandy JL, McDonell WN. Evaluation of concentrated solutions of guaifenesin for equine anesthesia. J Am Vet Med Assoc 1980;176: 619–622.
8. Lechner MD, Kreuscher H. Chemical compatibility of ketamine and midazolam in infusions solutions [in German]. Anaesthetist 1990;39: 62–65.
9. Hubbell JAE, Aarnes TK, Lerche P, Bednarski RM. Evaluation of a midazolam-ketamine-xylazine infusion for total intravenous anesthesia in horses. Am J Vet Res 2012;73:470–475.
10. Kerr CL, McDonell WN, Young SS. A comparison of romifidine and xylazine when used with diazepam/ketamine for short-duration anesthesia in the horse. Can Vet J 1996;37:601–609.
11. Yamashita K, Wijayathilaka TP, Kushiro T, Umar MA, Taguchi K, Muir WW. Anesthetic and cardiopulmonary effects of total intravenous anesthesia using a midazolam, ketamine and medetomidine drug combination in horses. J Vet Med Sci 2007;69:7–13.
12. McMurphy RM, Young LE, Marlin DJ, Walsh K. Comparison of the cardiopulmonary effects of anesthesia maintained by continuous infusion of romifidine, guaifenesin, and ketamine with anesthesia maintained by inhalation of halothane in horses. Am J Vet Res 2002; 63:1655–1661.
13. Lerche P. Total intravenous anesthesia in horses. Vet Clin North Am Equine Pract 2013;29:123–129.
14. Hubbell JAE, Kelly EM, Aarnes TK, et al. Pharmacokinetics of midazolam after intravenous administration to horses. Equine Vet J 2013;45:721–725.
15. Muir WW. Anxiolytics, nonopioid sedataive-analgesics, and opioid analgesics. In: Muir WW, Hubbell JAE, eds. Equine Anesthesia Monitoring and Emergency Therapy. 2nd ed. St. Louis, Missouri: Saunders Elsevier, 2009:185–209.
16. Johnson GM, Eastment JK, Wood JLN, Taylor PM. The confidential enquiry into perioperative equine fatalities (CEPEF): Mortality results of Phases 1 and 2. Vet Anaesth Analg 2002;29:159–170.
17. Steblaj B, Schauvliege S, Pavlidou K, et al. Comparison of respiratory function during TIVA (romifidine, ketamine, midazolam) and isoflurane anaesthesia in spontaneously breathing ponies Part I: Blood gas analysis and cardiorespiratory variables. Vet Anaesth Analg 2014;41:583–591.