FULL PAPER *Surgery*

Anesthetic and Cardiopulmonary Effects of Total Intravenous Anesthesia Using a Midazolam, Ketamine and Medetomidine Drug Combination in Horses

Kazuto YAMASHITA[1], Tikiri P. WIJAYATHILAKA[3], Tokiko KUSHIRO[4], Mohammed A. UMAR[1], Kiyoshi TAGUCHI[2] and William W. MUIR[4]

[1]*Departments of Small Animal Clinical Sciences and* [2]*Large Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyodai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan,* [3]*Department of Animal Production and Health, P. O. Box 13, Peradeniya 20400, Sri Lanka, Democratic Socialist Republic of Sri Lanka, and* [4]*Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210-1089, U.S.A.*

(Received 19 January 2006/Accepted 7 August 2006)

ABSTRACT. The anesthetic and cardiopulmonary effects of midazolam, ketamine and medetomidine for total intravenous anesthesia (MKM-TIVA) were evaluated in 14 horses. Horses were administered medetomidine 5 μg/kg intravenously as pre-anesthetic medication and anesthetized with an intravenous injection of ketamine 2.5 mg/kg and midazolam 0.04 mg/kg followed by the infusion of MKM-drug combination (midazolam 0.8 mg/ml-ketamine 40 mg/ml-medetomidine 0.1 mg/ml). Nine stallions (3 thoroughbred and 6 draft horses) were castrated during infusion of MKM-drug combination. The average duration of anesthesia was 38 ± 8 min and infusion rate of MKM-drug combination was 0.091 ± 0.021 ml/kg/hr. Time to standing after discontinuing MKM-TIVA was 33 ± 13 min. The quality of recovery from anesthesia was satisfactory in 3 horses and good in 6 horses. An additional 5 healthy thoroughbred horses were anesthetized with MKM- TIVA in order to assess cardiopulmonary effects. These 5 horses were anesthetized for 60 min and administered MKM-drug combination at 0.1 ml/kg/hr. Cardiac output and cardiac index decreased to 70–80%, stroke volume increased to 110% and systemic vascular resistance increased to 130% of baseline value. The partial pressure of arterial blood carbon dioxide was maintained at approximately 50 mmHg while the arterial partial pressure of oxygen pressure decreased to 50–60 mmHg. MKM-TIVA provides clinically acceptable general anesthesia with mild cardiopulmonary depression in horses. Inspired air should be supplemented with oxygen to prevent hypoxemia during MKM-TIVA.

KEY WORDS: equine, ketamine, medetomidine, midazolam, total intravenous anesthesia.

J. Vet. Med. Sci. 69(1): 7–13, 2007

Many surgical procedures and diagnostic examinations in horses are performed during general anesthesia in order to enhance their accuracy and maximize personal safety. Equine surgeons are often required to produce short-term anesthesia for purposes of castration, wound examination and treatment. Intravenous anesthesia is safe, simple to perform and does not require expensive or bulky equipment for its administration. The combination of guaifenesin, ketamine and α_2-adrenoceptor agonists (α_2-agonists: xylazine, detomidine, medetomidine, romifidine) has have been used for the prolongation of anesthesia in horses for a long time [14, 15, 29]. Total intravenous anesthesia (TIVA) using guaifenesin, ketamine and xylazine is a very popular anesthetic technique for producing short-term anesthesia in horses [14, 17, 29]. Anesthesia is produced by the combination of central nervous system (CNS) depression (ketamine, xylazine), muscular relaxation (guaifenesin, xylazine) and analgesia (ketamine, xylazine) [16, 17].

Unfortunately, there are no commercially available pharmaceutical preparations of guaifenesin in Japan. The central muscular relaxation produced by guaifenesin can be replaced by benzodiazepines, including diazepam [4], climazolam [1] and midazolam [5, 9, 12]. Midazolam may be one of the most useful injectable benzodiazepine because it is water-soluble. The CNS depression and analgesic effects produced by xylazine can be replaced by more potent α_2-agonists, including detomidine [22, 23], romifidine [8, 15] and medetomidine [26]. Medetomidine has a higher α_2-adrenoceptor selectivity than xylazine and detomidine [10, 24] and produces sedative and analgesic effects at smaller doses than xylazine and detomidine in horses [25, 26]. We hypothesized that a midazolam-ketamine- medetomidine (MKM) drug combination would provide safe and effective short-term anesthesia similar to that produced using a guaifenesin-ketamine-xylazine drug combination. Therefore, we determined the anesthetic and cardiopulmonary effects of TIVA using MKM-drug combination (MKM-TIVA) in horses subjected to surgical castration and five normal healthy horses, respectively.

MATERIALS AND METHODS

Evaluation of MKM-TIVA for Surgical Castration: Nine stallions (3 thoroughbred and 6 draft horses) admitted to the Rakuno Gakuen University Veterinary Teaching Hospital between August 2002 and December 2004 were castrated outside of the hospital building under MKM-TIVA. All horses were healthy and free from clinically important cardiovascular and respiratory tract diseases. Body weight ranged from 266 to 900 kg (652 ± 253 kg) and age ranged from 1 to 11 years (4.5 ± 4.1 years). Food, but not water, was withheld from the horses for a minimum of 8 hr before anesthesia.

A 14-gauge catheter (Angiocath, Becton Dickinson

Table 1. Criteria for scoring the quality of anesthetic induction, maintenance and recovery in horses anesthetized with MKM-TIVA

Score	Criteria
Anesthetic induction	
0 (Poor)	Ataxia, paddling, danger to horse and handler.
1 (Fair)	Purposeful paddling with or without attempts to regain feet.
2 (Satisfactory)	Ataxia with or without paddling.
3 (Good)	Takes one or two steps before falling to ground. No paddling.
4 (Excellent)	Sinks smoothly to ground.
Anesthetic maintenance	
0 (Poor)	Difficult to maintain surgical anesthesia.
1 (Fair)	Required multiple drug increments.
2 (Good)	Appeared light. Responded to three or four drug increments.
3 (Excellent)	Smooth. Responded to one or two drug increments.
Anesthetic recovery	
0 (Unable to stand)	Animal can not stand over 2 hr following multiple attempts to stand. Excitement is evident. Injury or high risk of injury.
1 (Poor)	Multiple attempts to stand. Excitement is evident. High risk of injury.
2 (Fair)	Multiple attempts to stand. Significant ataxia.
3 (Satisfactory)	Stands after one to three attempts. Prolonged ataxia but with no excitement.
4 (Good)	Stands after one or two attempts with mild short-lived ataxia.
5 (Excellent)	Stands after first attempt. No ataxia.

Modified from the criteria for scoring system reported by Yamashita, *et al.* [26].

Japan, Inc., Tokyo, Japan) was placed in the left jugular vein in all horses. The horses were pre-medicated with intravenous injection (IV) of medetomidine (5 μg/kg) (Domitor, Meiji Seika Co., Tokyo, Japan). Anesthesia was induced with midazolam (0.04 mg/kg, IV) (Dormicum, Yamanouchi Pharmaceutical Co., Tokyo, Japan) and ketamine (2.5 mg/kg, IV) (Ketalar 100, Sankyo Co., Tokyo, Japan). The quality of induction was scored (Table 1). The horses were orotrachealy intubated and breathed air. MKM-drug combination (midazolam 0.8 mg/m*l*, ketamine 40 mg/m*l* and medetomidine 0.1 mg/m*l*) that was prepared up to 50 m*l* of final volume in a plastic syringe was infused (0.05 m*l*/kg/hr) using a syringe infusion pump (STC-521, Terumo, Tokyo, Japan) immediately following the orotracheal intubation. The horses were positioned in dorsal recumbency in a grass field and castrated (open castration) by an experienced veterinary surgeon. Small incremental doses of MKM-drug combination (0.01 m*l*/kg bolus IV) were administered to maintain surgical anesthesia when horses showed purposeful responses to surgical stimulation or eye signs such as strong rapid nystagmus. The MKM-drug combination requirement for maintaining surgical anesthesia was calculated as the mean infusion rate (m*l*/kg/hr) from the total amount of MKM-drug combination administered by infusion plus the incremental bolus doses. Pulse rate (PR; beats/min) and respiratory rate (RR; breaths/min) were recorded throughout anesthesia. The PR was determined by palpation on the facial artery. RR was determined by observing chest wall movement. The quality of the maintenance phase of surgical anesthesia was scored (Table 1).

Recovery was considered to begin when the infusion of MKM-drug combination was discontinued. The horses were positioned in right lateral recumbency on the grass field and allowed to recover unassisted. The endotracheal tube was removed when horses regained swallowing reflex. The times to extubation, the first movement of the head or limbs, sternal recumbency without returning to lateral recumbency and standing without returning to recumbency were recorded. The quality of recovery was scored (Table 1).

After the surgery, all horses received flunixin meglumine (1 mg/kg, IV) (Banamine, Dainippon Pharmaceutical Co., Osaka, Japan) and intramuscular injection of benzyl penicillin (4,000,000 Units/head) combined with dihydrostreptomycin sulfate (5,000 mg/head) (Mycillinsol Meiji, Meiji Seika Co.) for 3 days twice a day as post-operative treatments.

Evaluation of MKM-TIVA cardiopulmonary effects: The cardiopulmonary effects of *MKM-TIVA* were assessed in 5 healthy thoroughbred horses (one stallion and 4 geldings). Body weight ranged from 442 to 560 kg (497 ± 44 kg) and age ranged from 3 to 11 years (6.2 ± 3.0 years). All horses were cared for according to the principles of the 'Guide for the Care and Use of Laboratory Animals' prepared by Rakuno Gakuen University. Their right carotid arteries had been surgically repositioned to a subcutaneous location under general anesthesia at least one month before being assigned to this study. Food, but not water, was withheld from the horses for a minimum of 8 hr before anesthesia.

The horses were restrained in wooden stocks to facilitate placement of vascular catheters and record baseline hemodynamic data. The area over the repositioned right carotid artery and right and left jugular furrows were clipped and prepared aseptically, and approximately 1 m*l* of 2% lidocaine (Xylocaine, Fujisawa Pharmaceutical Co. Osaka, Japan) was injected subcutaneously at each catheter site. A 14-gauge catheter (Angiocath, Becton Dickinson Japan, Inc.) was aseptically placed in the left jugular vein. An 18-

gauge catheter (Supercath, Medikit Co., Tokyo, Japan) was aseptically placed in the raised right carotid artery. An 8-french introducer (Exacta percutaneous sheath introducer, Ohmeda, West Yorkshire, U.K.) was aseptically placed in the right jugular vein. A 9-french introducer (Exacta percutaneous sheath introducer, Ohmeda) was aseptically placed in the right jugular vein 30 cm cranial to the 8-french introducer. A 7-french thermodilution catheter (Criti-Cath SP-5107, Ohmeda) was aseptically placed in the pulmonary artery through the 8-french introducer. An 8-french catheter 100 cm in length (Intervec super guiding catheter, Fuji Systems Co., Tokyo, Japan) was aseptically placed in the right atrium through the 9-french introducer. The distance between the tips of thermodilution catheter and the 8-french catheter was adjusted to 40–50 cm.

Baseline values of cardiopulmonary parameters were recorded in all horses while resting in the stocks. Arterial blood pressure (ABP; mmHg), pulmonary artery pressure (PAP; mmHg), and right atrial pressure (RAP; mmHg) were determined by connecting the catheters placed in the raised carotid artery, the pulmonary artery, and the right atrium, respectively, to pressure transducers (CDX-A90, Cobe Laboratories, Tokyo, Japan). Cardiac output (CO; L/min) was determined by the thermodilution technique [20]. A volume of 40 m*l* of 0°C 5% dextrose was injected manually in approximately 2 sec through the 8-french catheter placed in the right atrium. Temperature fluctuation was detected using the thermodilution catheter placed in the pulmonary artery. The CO was measured three times, and the mean value of three values was calculated. Rectal temperature (RT; °C), heart rate (HR; beats/min), ECG (Apex-Base lead), ABP, PAP, RAP and CO were recorded by physiologic display and recording system (DS-5300, Fukuda Denshi, Tokyo, Japan). The RR was determined by observing chest wall movement. Cardiac index (CI; m*l*/kg/min) was calculated from the body weight and CO; stroke volume (SV; m*l*/beat) was calculated from the HR and CO; and peripheral vascular resistance (SVR; dynes•sec•cm^{-5}) was determined from the mean ABP, CO and mean RAP [2]. Arterial blood samples were anaerobically obtained from the 18-gauge catheter placed in the right carotid artery and analyzed for pH and the partial pressure of oxygen (PaO_2; mmHg) and carbon dioxide ($PaCO_2$; mmHg) by a blood gas analyzer (Rapidlab 348, Bayer Medical Co., Tokyo, Japan).

After the baseline data was collected, the horses were premedicated and induced to anesthesia using the same anesthetic protocol as the horses that were castrated. All horses were positioned in left lateral recumbency on a 30 cm thick foam pad and maintained under general anesthesia for 60 min with the infusion of MKM-drug combination at 0.1 m*l*/kg/hr. All horses breathed room air throughout anesthesia and recovery. Cardiovascular measurements and arterial blood gas analysis were recorded every 10 min during anesthesia. After recording the data at 60 min of anesthesia, the monitoring equipment was disconnected and the infusion of MKM-drug combination was discontinued. Then, the horses were transported to a 2.5 m × 2.5 m padded recovery stall. All horses were recovered unassisted. The times to the extubation, first movement, a sternal position, and standing after the cessation of the MKM-drug combination were recorded. The quality of recovery was categorically evaluated (Table 1).

Statistical analysis: Data are shown as mean ± standard deviation. A one-way repeated measures analysis of variance (ANOVA) was used to analyze the changes in cardiopulmonary parameters during anesthesia. A paired *t*-test was also used to compare the baseline value and each data recorded during anesthesia. Differences were considered significant when $p<0.05$.

RESULTS

Anesthetic effects of MKM-TIVA: The infusion of MKM-drug combination provided good anesthesia for castration and uneventful recovery in all horses. Induction of anesthesia was excellent in 8 horses and good in a horse. The average time from induction to the cessation of anesthesia was 38 ± 8 min (range, 30 to 54 min). All horses received additional IV doses of the MKM-mixture drug combination in order to maintain surgical anesthesia (one dose in 2 horses, two doses in 3 horses, three doses in 2 horses and four doses in a horse). The requirement of total MKM-drug combination in order to maintain surgical anesthesia averaged 0.091 ± 0.021 m*l*/kg/hr. Based on this data, we decided to administer 0.1 m*l*/kg/hr of MKM-drug combination for the cardiopulmonary study. There was no significant change in PR and RR during anesthesia. PR remained between 30 to 40 beats/min. All horses breathed spontaneously at 15 to 20 breaths/min (Fig. 1).

The times to the extubation, first movement, sternal position and standing after the cessation of anesthesia ranged from 3 to 25 min, 11 to 35 min, 18 to 35 min and 20 to 58 min, respectively. Seven horses stood at their first attempt. Another 2 horses stood on their second and third attempts. All horses displayed mild to moderate ataxia after standing.

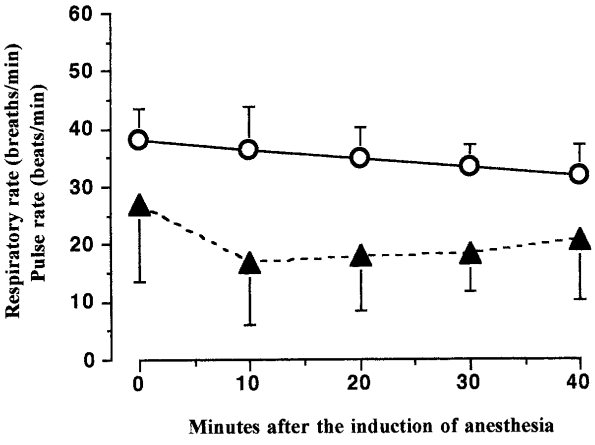

Fig. 1. Changes in pulse rate (○) and respiratory rate (▲) in horses castrated under MKM-TIVA. Each plot and error bar showed mean value and standard deviation from 9 horses.

Table 2. Total anesthesia time, infusion rate of MKM-drug combination, quality of anesthesia, recovery times and number of attempts to stand in horses anesthetized with MKM-TIVA

	Castration cases	Cardiopulmonary study
Number of horses	9	5
Total anesthesia time (min)	38 ± 8	60
Infusion rate (ml/kg/hr)	0.091 ± 0.021	0.1
Quality of anesthesia (score) *		
Induction	4 (3–4)	4 (4)
Maintenance	3 (2–3)	3 (3)
Recovery	4 (3–4)	4 (3–4)
Recovery times (min)†		
Extubation	16 ± 6	16 ± 13
First movement	21 ± 7	24 ± 11
Sternal position	24 ± 7	41 ± 26
Standing	33 ± 13	59 ± 22
Number of attempts to stand	1 (1–3)	2(1–3)

Data are given as mean ± standard deviation or median (range).
* See Table 1 for scoring criteria. † Times are recorded from the time infusion of MKM-drug combination was discontinued.

Table 3. Changes in cardiopulmonary parameters in horses anesthetized with MKM-TIVA

	Baseline	Time of MKM infusion (min)					
		10	20	30	40	50	60
Rectal Temperature (°C)**	37.8±0.4	36.7±0.3[a]	36.6±0.3[b]	36.5±0.3[b]	36.4±0.3[b]	36.3±0.4[b]	36.3±0.4[b]
HR (beats/min)**	44±6	32±5[b]	32±2[b]	32±2[b]	33±3[a]	33±3[b]	33±4[b]
RR (breaths/min)	14±3	15±9	15±8	14±10	13±5	14±5	15±10
MABP (mmHg)	138±17	132±7	126±9	130±12	129±17	131±17	128±18
MPAP (mmHg)**	26±3	14±8[a]	13±8[a]	15±10	17±9	15±9	15±8[a]
MRAP (mmHg)	18±5	12±10	10±10	13±14	12±11	13±11	13±11
CO (L/min)**	29.3±5.7	19.0±4.0[b]	19.8±3.8[b]	21.9±2.0[b]	23.2±3.4[b]	25.1±2.7	24.2±4.6[b]
CI (ml/min/kg)**	60.7±7.6	38.3±8.0[b]	39.6±5.2[b]	44.2±4.7[b]	46.8±6.5[b]	50.4±1.7[a]	48.6±8.2[a]
SV (ml/beat)*	671±118	614±167	617±97	676±58	717±119	758±74[b]	742±167
SVR (dynes•sec•cm^{-5})**	331±45	526±120[a]	482±104[a]	428±25[b]	408±59[a]	379±42	392±73
Arterial blood pH	7.408±0.016	7.390±0.027	7.407±0.017	7.437±0.081	7.447±0.058	7.444±0.071	7.428±0.026
$PaCO_2$ (mmHg)	46.8±2.5	51.9±4.4	49.3±2.9	45.9±11.1	44.9±8.4	43.9±9.1	47.5±5.3
PaO_2 (mmHg)**	100.9±9.1	51.5±13.5[b]	60.5±6.5[b]	55.4±5.1[b]	58.7±8.3[b]	54.1±7.6[b]	50.9±7.7[b]

Data: mean ± standard deviation. HR: heart rate, RR: respiratory rate, MABP: mean arterial blood pressure, MPAP: mean pulmonary artery pressure, MRAP: mean right atrial pressure, CO: cardiac output, CI: cardiac index, SV: stroke volume, SVR: systemic vascular resistance, $PaCO_2$: partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen. Significant difference was detected by one-way repeated-measure ANOVA: *$p < 0.05$, ** $p < 0.01$. Significant difference from the baseline value was detected by paired t-test: [a] $p<0.05$, [b] $p<0.01$.

The quality of recovery was good in 6 horses and satisfactory in 3 horses (Table 2).

Cardiopulmonary effects of MKM-TIVA: The infusion of the MKM-drug combination produced measurable hemodynamic effects (Table 3). The RT decreased significantly but remained over 36.0°C during anesthesia. The HR, CO and CI decreased significantly and shortly after initiating anesthesia but remained at 70–80% of the the baseline values. The SV increased significantly to 110% of the baseline values. The SVR increased significantly to 130% of the baseline values, then gradually recovered returned to the baseline values. Mean PAP decreased significantly and averaged 13–17 mmHg. There was no significant change in mean ABP and RAP.

All horses breathed spontaneously and RR averaged 13–15 breaths/min. There were significant changes in RR, arterial blood pH and $PaCO_2$. The PaO_2 decreased significantly and remained between 50–60 mmHg during anesthesia.

The times to the extubation, first movement, sternal position and standing ranged from 4 to 32 min, 7 to 38 min, 9 to 77 min and 36 to 88 min, respectively. A horse stood on the first attempt, 3 horses stood on their second attempt and a horse stood on the third attempt. All horses displayed mild to moderate ataxia after standing. The quality of recovery was good in 3 horses and satisfactory in 2 horses (Table 2).

DISCUSSION

Our data indicate that MKM-TIVA provides effective general anesthesia for castration in horses with minimal changes in cardiopulmonary function. The qualities of induction and maintenance of anesthesia were good to excellent in all horses castrated under MKM-TIVA. The infusion (0.05 m*l*/kg/hr) and small incremental bolus doses (0.01 m*l*/kg bolus IV) of MKM-drug combination provided uneventful surgical anesthesia without side effect. The constant rate infusion of MKM-drug combination at 0.1 m*l*/kg/hr (midazolam 0.08 mg/kg/hr, ketamine 4 mg/kg/hr and medetomidine 10 μg/kg/hr) suggests that stable surgical anesthesia can be provided as evidenced by the MKM-drug combination requirement for castration (0.091 ± 0.021 m*l*/kg/hr).

The technique of TIVA using a mixture of guaifenesin (100 mg/m*l*), ketamine (2 mg/m*l*) and xylazine (1 mg/m*l*) has been used and promoted for several decades as a method of producing equine anesthesia [6, 17, 29]. Taylor *et al.* [22, 23] reported TIVA using a mixture of guaifenesin (100 mg/m*l*), ketamine (4 mg/m*l*) and detomidine (40 μg/m*l*) in ponies. Brock and Hildebrand [3] reported that diazepam (0.1 mg/kg) could be substituted for guaifenesin (100 mg/kg) in horses. In our clinical experiences, the water-soluble benzodiazepine midazolam (0.04 mg/kg IV) can be substituted for diazepam (0.1 mg/kg) or guaifenesin (50 mg/kg IV) when administered in combination with ketamine or thiopental in horses. The sedative effects of medetomidine, 10 μg/kg IV, are similar to or somewhat more potent than xylazine, 1 mg/kg IV, or detomidine, 40 μg/kg IV [25]. Based on these earlier findings we estimated that the concentration of drugs in the MKM-drug combination to be midazolam 0.8 mg/m*l*-ketamine 40 mg/m*l*- medetomidine 0.1 mg/m*l*.

Young *et al.* [29] reported that surgical anesthesia for elective surgeries in horses could be maintained with TIVA using a mixture of guaifenesin (100 mg/m*l*), ketamine (2 mg/m*l*) and xyazine (1 mg/m*l*) at infusion rates varying from 1.0–1.4 m*l*/kg/hr (guaifenesin 100–110 mg/kg/hr, ketamine 2.0–2.8 mg/kg/hr and xylazine 1.0–1.4 mg/kg/hr). Taylor *et al.* [22] reported that surgical anesthesia for castration could be maintained in ponies using a mixture of guaifenesin (100 mg/m*l*), ketamine (4 mg/m*l*) and detomidine (40 μg/m*l*) at an infusion rate of 0.8 m*l*/kg/hr (guaifenesin 80 mg/kg/hr, ketamine 3.2 mg/kg/hr and detomidine 32 μg/kg/hr). Recently, Kushiro *et al.* [9] reported that midazolam 0.02 mg/kg/hr could be substituted for guaifenesin 25 mg/kg/hr in horses. In this study, surgical anesthesia for castration was achieved by infusing MKM-drug combination at 0.091 ± 0.021 m*l*/kg/hr. The infusion of MKM-drug combination at 0.1 m*l*/kg/hr (midazolam 0.08 mg/kg/hr, ketamine 4 mg/kg/hr and medetomidine 10 μg/kg/hr) can be expected to provide an equipotent anesthetic effect with TIVA similar to that provided by mixtures of guaifenesin-ketamine-xylazine and guaifenesin-ketamine-detomidine.

TIVA with guaifenesine-ketamine-xylazine is characterized by active palpebral reflexes, variable degrees of nystagmus, occasional swallowing reflexes and ear movement [29]. The persistence of these reflexes is inconsequential, except in the case of laryngeal surgery. MKM-TIVA was also characterized by these reflexes except for swallowing reflex. Endotracheal intubation had been maintained without strong swallowing reflex in all horses during MKM infusion. Midazolam is a centrally acting muscular relaxant similar to guaifenesin, however, it produces more potent anesthetic and muscular relaxant effects in horses, compared to guaifenesin [5]. Midazolam might provide the depression of swallowing reflex during MKM-TIVA. Further study is required to confirm the effect of MKM-drug combination on the swallowing reflex.

TIVA has been advocated as alternative and possibly superior method of producing equine anesthesia in horses on the basis of cardiopulmonary, endocrine and economic data [1, 22, 23]. Studies investigating the anesthetic potential of various combinations of α_2-agonists (e.g. xylazine, detomidine, romifidine, medetomidine), dissociative anesthetics (e.g. ketamine, tiletamine) and muscle relaxing drugs (e.g, . guaifenesin, diazepam, climazolam, midazolam, zolazepam) for producing TIVA in horses have generally demonstrated less cardiovascular depression compared with inhalation anesthesia [1, 6, 8, 13, 15, 19, 22, 23]. We observed minimal cardiovascular changes using MKM-TIVA in horses, such as mild decreases in heart rate, cardiac output and cardiac index and mild increases in stroke volume and systemic vascular resistance. Midazolam produces minimum cardiopulmonary effects [16] and minimal decreases in arterial blood pressure in horses [5, 12]. Medetomidine produces decreases in heart rate, cardiac output and increase in systemic vascular resistance by activating central and peripheral α_2-adrenoceptors [16, 27]. Increase in systemic vascular resistance after the IV administration of medetomidne produces a short-lived hypertensive phase accompanied by a compensatory baroreceptor-mediated reflex bradycardia [16, 27]. The cardiovascular actions of ketamine include increases in heart rate and cardiac output which are attributed to increase in centrally mediated sympathetic tone, release of catecholamines from peripheral storage sites, inhibition of neural, extraneural uptake of chatecholamines and inhibition of baroreceptor reflex activity [11, 17, 19]. Ketamine also produces direct vasodilation of vascular smooth muscle and an inotropic effect on the myocardium [11]. The cardiovascular stimulating effects induced by ketamine are blunted or prevented by prior administration of benzodiazepines and α_2-agonists [11]. Therefore, we considered that the cardiovascular changes observed in horses anesthetized with MKM-TIVA were a result of the additive and synergistic effects midazolam, ketamine and medetomidine. Our results indicate that the MKM-TIVA can provide general anesthesia for approximately 1 hr with minimum cardiovascular depression in horses.

We elected not to administer supplemental oxygen in order to more closely mimic field nesthesia where oxygen is not routinely administered. During MKM-TIVA, all horses

breathed room air spontaneously and the $PaCO_2$ and arterial pH remained within normal limits. The PaO_2 decreased significantly and significant hypoxemia was observed in all horses. Similar respiratory changes have been reported in horses breathing room air during TIVA using infusions of ketamine and xylazine [15] and short duration anesthesia produced by romifidine or xylazine with diazepam and ketamine [8]. A combination of intrapulmonary vascular shunting, ventilation-perfusion mismatching, and hypoventilation are the predominant causes of the hypoxemia in horses [21]. Our data suggests that there was no change or only a minimal decrease in alveolar ventilation during MKM-TIVA because $PaCO_2$ values remained within acceptable range during anesthesia. Therefore, the reduction of PaO_2 during MKM-TIVA might be attributed to the combination of intrapulmonary vascular shunting and ventilation-perfusion mismatching. Because there was a minimal cardiovascular depression during MKM-TIVA, increasing the inspired oxygen concentration may have been an effective method to minimize the reduction of PaO_2. Although no overt problems attributable to hypoxemia were observed in any horse, supplemental oxygen is recommended during MKM-TIVA.

Young and Taylor [30] reported that improved recovery from anesthesia is associated with shorter, less invasive surgical procedures and a slower recovery in horses. Hypotension during anesthesia is one of the main causes of severe post-operative myopathy in horses [18, 30]. Recovery from MKM-TIVA was uneventful and judged to be clinically acceptable. The recovery times we determined were comparable or slightly longer than those previously reported after TIVA with different drug combinations in horse [14, 19, 22, 29]. The recovery time may equal to or exceed the total duration of anesthesia when MKM-TIVA is prolonged. Short-term anesthesia, comparatively slow recovery and minimal cardiovascular depression might bring about uneventful recoveries in this study.

The quality of recovery from MKM-TIVA in our study ranged from good to satisfactory primarily because of the presence of ataxia. The tendency to display ataxia after standing is relatively common in horses pre-medicated with midazolam [5]. Similar observations have been made after short-term anesthesia of horses administered other benzodiazepine combinations, such as tiletamine and zolazepam [19]. Ataxia has also been reported in horses anesthetized with ketamine and climazolam, and the benzodiazepine antagonist, sarmazenil, has been successfully used to overcome it [1]. Sarmazenil completely reversed the depressive effects on electroencephalogram induced by midazolam [7]. The CNS depression, ataxia and cardiopulmonary effect induced by medetomidine can be reversed with atipamezole in horses [28]. However, this must be done cautiously in order to avoid the hallucinatory behavior and muscular rigidity induced by ketamine [11, 17]. Further studies are needed regarding the timing of the administration of selective antagonists to enhance the recovery from MKM-TIVA in horses.

The MKM-drug combination used in this study can be prepared by mixing pharmaceutical preparations of midazolam (5 mg/m*l*) 8 m*l*, ketamine (100 mg/m*l*) 20 m*l* and medetomidine (1 mg/m*l*) 5 m*l*, respectively. The final volume of MKM-drug combination is then adjusted by adding saline or isotonic fluid. The standard infusion rate of MKM-mixture may be 0.1 m*l*/kg/hr when the final volume is adjusted to 50 m*l* to complete a final mixture containing midazolam 0.8 mg/m*l*, ketamine 40 mg/m*l* and medetomidine 0.1 mg/m*l*. The standard infusion rate can be increased to 1 m*l*/kg/hr, if the final volume of the mixture is adjusted to 500 m*l*. We believe that MKM-TIVA is an effective and convenient protocol for producing equine anesthesia, because of comparative simplicity of preparation, safety and economy compared to the mixture of guaifenesin, ketamine and xylazine or detomidine.

In conclusion, MKM-TIVA provides good to excellent surgical anesthesia for minor surgical procedures such as castration in horses with minimal cardiopulmonary depression except hypoxemia. The quality of surgical anesthesia, coupled with manageable recoveries and uncomplicated preparation of drug mixture, suggests that MKM-TIVA has considerable promise as an injectable technique that can be used to produce extended anesthesia under field conditions. Inspired air should be supplemented with oxygen to prevent hypoxemia.

REFERENCES

1. Bettschart-Wolfensberger, R., Taylor, P.M., Sear, J.W., Bloomfield, M. R., Rentsch, K. and Dawling, S. 1996. Physiologic effects of anesthesia induced and maintained by intravenous administration of a climazolam-ketamine combination in ponies premedicated with acepromazine and xylazine. *Am. J. Vet. Res.* **57**: 1472–1477.
2. Bonagura, J. D. and Muir, W. W 1991. The cardiovascular system. pp. 38–101. In: Equine Anesthesia: Monitoring and Emergency Therapy (Muir, W. W. and Hubbell, J. A. E. eds.), Mosby-Year Book, St. Louis.
3. Brock, N. and Hildebrand, S. V. 1990. A comparison of xylazine-diazepam- ketamine and xylazine-guaifenesin-ketamine in equine anesthesia. *Vet. Surg.* **19**: 468–474.
4. Flaherty, D., Reid, J., Welsh, E., Monteiro, A.M., Lerche, P. and Nolan, A. 1997. A pharmacodynamic study of propofol or propofol and ketamine infusions in ponies undergoing surgery. *Res. Vet. Sci.* **62**: 179–184.
5. Gangl, M., Grulke, S., Detilleux, J., Caudron, I. and Serteyn, D. 2001. Comparison of thiopentone/guaifenesin, ketamine/guaifenesin and ketamine/midazolam for the induction of horses to be anaesthetised with isoflurane. *Vet. Rec.* **149**: 147–151.
6. Greene, S. A., Thurmon, J. C., Tranquilli, W. J. and Benson, G. J. 1986. Cardiopulmonary effects of continuous intravenous infusion of guaifenesin, ketamine, and xylazine in ponies. *Am. J. Vet. Res.* **47**: 2364–2367.
7. Johnson, C. B., Bloomfield, M. and Taylor, P. M. 2003. Effects of midazolam and sarmazenil on the equine electroencephalogram during anaesthesia with halothane in oxygen. *J. Vet. Pharmacol. Ther.* **26**: 105–112.
8. Kerr, C. L., McDonell, W. N. and Young, S. S. 1996. A com-

parison of romifidine and xylazine when used with diazepam/ketamine for short duration anesthesia in the horse. *Can. Vet. J.* **37**: 601–609.
9. Kushiro, T., Yamashita, K., Umar, M. A., Maehara, S., Wakaiki, S., Abe, R., Seno, T., Tsuzuki, K., Izumisawa, Y. and Muir, W. W. 2005. Anesthetic and cardiovascular effects of balanced anesthesia using constant rate infusion of midazolam-ketamine-medetomidine with inhalation of oxygen-sevoflurane (MKM-OS anesthesia) in horses. *J. Vet. Med. Sci.* **67**: 379–384.
10. Lamont, L. and Tranquilli, W. 2002. α_2-Agonists. pp. 199–220. *In*: Handbook of Veterinary Pain Management. (Gaynor, J. S. and Muir, W. W. eds.), Mosby, St. Louis.
11. Lin, H. C. 1996. Dissociative anesthetics. pp. 241–296. *In*: Lumb & Jones' Veterinary Anesthesia, 3rd ed. (Thurmon, J. C., Tranquilli, W. J. and Benson, G. J. eds.), Williams and Wilkins, Baltimore.
12. Luna, S.P., Taylor, P.M. and Massone, F. 1997. Midazolam and ketamine induction before halothane anaesthesia in ponies: cardiorespiratory, endocrine and metabolic changes. *J. Vet. Pharmacol. Ther.* **20**: 153–159.
13. Mama, K. R., Wagner, A. E., Steffey, E. P., Kollias-Baker, C., Hellyer, P. W., Golden, A. E. and Brevard, L. F. 2005. Evaluation of xylazine and ketamine for total intravenous anesthesia in horses. *Am. J. Vet. Res.* **66**: 1002–1007.
14. McCarty, J. E., Trim, C. M. and Ferguson, D. 1990. Prolongation of anesthesia with xylazine, ketamine, and guaifenesin in horses: 64 cases (1986–1989). *J. Am. Vet. Med. Assoc.* **197**: 1646–1650.
15. McMurphy, R. M., Young, L. E., Marlin, D. J. and Walsh, K. 2002. 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.* **63**: 1655–1661.
16. Muir, W. W 1991. Standing chemical restraint in horses; tranquilizers, sedatives, and analgesics. pp. 239–272. *In*: Equine Anesthesia: Monitoring and Emergency Therapy (Muir, W. W. and Hubbell, J. A. E. eds.), Mosby-Year Book, St. Louis.
17. Muir, W. W 1991. Intravenous anesthetics and anesthetic techniques in horses. pp. 273–300. *In*: Equine Anesthesia: Monitoring and Emergency Therapy (Muir, W. W. and Hubbell, J. A. E. eds.), Mosby-Year Book, St. Louis.
18. Muir, W. W 1991. Complications: induction, maintenance, and recovery phases of anesthesia. pp. 406–429. *In*: Equine Anesthesia: Monitoring and Emergency Therapy (Muir, W. W. and Hubbell, J. A. E. eds.), Mosby-Year Book, St. Louis.
19. Muir, W. W., Lerche, P., Robertson, J. T., Hubbell, J. A., Beard, W., Miller, T., Badgley, B. and Bothwell, V. 2000. Comparison of four drug combinations for total intravenous anesthesia of horses undergoing surgical removal of an abdominal testis. *J. Am. Vet. Med. Assoc.* **217**: 869–873.
20. Muir, W. W., Skarda, R. T., and Milne, D. W. 1976. Estimation of cardiac output in the horse by thermodilution techniques. *Am. J. Vet. Res.* **37**: 697–700.
21. Robinson, N. E. 1991. The respiratory system. pp. 7–37. *In*: Equine Anesthesia: Monitoring and Emergency Therapy (Muir, W. W. and Hubbell, J. A. E. eds.), Mosby-Year Book, St. Louis.
22. Taylor, P. M., Kirby, J. J., Shrimpton, D. J. and Johnson, C. B.1998. Cardiovascular effects of surgical castration during anaesthesia maintained with halothane or infusion of detomidine, ketamine and guaifenesin in ponies. *Equine Vet. J.* **30**: 304–309.
23. Taylor, P. M.. Luna, S. P., Sear, J. W. and Wheeler, M. J. 1995. Total intravenous anaesthesia in ponies using detomidine, ketamine and guaiphenesin: pharmacokinetics, cardiopulmonary and endocrine effects. *Res. Vet. Sci.* **59**: 17–23.
24. Virtanen, R., Savola, J. M., Saano, V. and Nyman, L. 1988. Characterization of the selectivity, specificity, and potency of medetomidine as an α_2-adrenoceptor agonists. *Eur. J. Pharmacol.* **150**: 9–14.
25. Yamashita, K., Kishihara, K., Maki, S., Haramaki, S., Tsukiyama, K., Tagami, M., Izumisawa, Y. and Kotani, T. 1999. Comparison of the sedative effects of medetomidine, detomidine, and xylazine in horses. *J. Jpn. Vet. Med. Assoc.* **52**: 498–503 (in Japanese with English summary).
26. Yamashita, K., Muir, W. W., Tsubakishita, S., Abrahamsen, E., Lerch, P., Hubbell, J. A., Bednarski, R. M., Skarda, R. T., Izumisawa, Y. and Kotani, T. 2002. Clinical comparison of xylazine and medetomidine for premedication of horses. *J. Am. Vet. Med. Assoc.* **221**: 1144–1149.
27. Yamashita, K., Tsubakishita, S., Futaoka, S., Ueda, I., Hamaguchi, H., Seno, T., Katoh, S., Izumisawa. Y., Kotani, T. and Muir, W. W. 2000. Cardiovascular effects of medetomidine, detomidine and xylazine in horses. *J. Vet. Med. Sci.* **62**: 1025–1032.
28. Yamashita, K., Yonezawa, K., Izumisawa. Y. and Kotani, T. 1996. Antagonistic effects of atipamezole on medetomidine-induced sedation in horses. *J. Vet. Med. Sci.* **58**: 1049–1052.
29. Young, L. E., Bartram, D. H., Diamond, M. J., Gregg, A. S., Jones, R. S. 1993. Clinical evaluation of an infusion of xylazine, guaifenesin and ketamine for maintenance of anaesthesia in horses. *Equine Vet. J.* **25**: 115–119.
30. Young, S. S. and Taylor, P. M. 1993. Factors influencing the outcome of equine anesthesia: a review of 1,314 cases. *Equine Vet. J.* **25**: 147–151.