ARTICLE

A comparison of romifidine and xylazine when used with diazepam/ketamine for short duration anesthesia in the horse

Carolyn L. Kerr, Wayne N. McDonell, Simon S. Young

Abstract

The purpose of this study was to compare and evaluate sedation with intravenous xylazine (1.1 mg/kg bodyweight [BW]) versus intravenous romifidine (100 µg/kg BW) followed by induction of anesthesia with intravenous diazepam (0.04 mg/kg BW) and ketamine (2.2 mg/kg BW). Twelve healthy horses were used in a blinded, randomized, cross-over design. Heart rate, presence of 2nd degree atrioventricular heart blocks (2°AVB), respiratory rate, arterial blood pressures, blood gases, packed cell volume, total serum proteins, and duration of anesthesia and recumbency were recorded. Induction and recovery quality was evaluated using a 0 to 4 score. Response to stimulation with noise, pressure, and cutaneous electrical stimulation was assessed at 5 minute intervals during recumbency to evaluate the depth of anesthesia. Heart rate was lower and 2°AVB more frequent in the romifidine group, while blood pressure was lower in the xylazine group. Duration of anesthesia was longer in the romifidine group ($\bar{x}$ 20.8, $s_{\bar{x}}$ 2.3 min) versus the xylazine group ($\bar{x}$ 15.8, $s_{\bar{x}}$ 1.6 min), while induction and recovery were excellent in both groups. Respiratory rates, blood gas values, packed cell volumes, and total protein levels did not differ between groups. The results indicate that romifidine premedication followed by diazepam and ketamine is a very satisfactory regime for short duration intravenous anesthesia in horses.

Résumé

Comparaison entre la romifidine et la xylazine, en association avec le diazépam et la kétamine, lors d'anesthésies de courtes durées chez le cheval

L'objectif de cette étude était de comparer et d'évaluer la sédation produite par l'administration intraveineuse de xylazine (1,1 mg/kg de poids vif [PV]) à celle produite par la romifidine (100 µg/kg PV) administrée de la même façon et suivie par une induction de l'anesthésie par le diazépam (0,04 mg/kg PV) et la kétamine (2,2 mg/kg PV), administrés par voie intraveineuse. Douze chevaux en santé ont été utilisés dans un modèle, aléatoire, croisé, et à l'aveugle. La fréquence cardiaque, la présence d'un bloc auriculoventriculaire du deuxième degré (BAV 2°), la fréquence respiratoire, la pression sanguine artérielle, le volume des éléments figurés du sang, les protéines sériques totales et la durée de l'anesthésie et du décubitus ont été enregistrés. La qualité de l'induction et du réveil a été évaluée sur une échelle de 0 à 4. Pendant la période de décubitus, la profondeur de l'anesthésie a été vérifiée à des intervalles de 5 minutes en mesurant la réponse au bruit, à la pression et à la stimulation électrique de la peau. La fréquence cardiaque était plus basse et les BAV 2° plus fréquents dans le groupe de la romifidine alors que la pression sanguine était plus basse dans le groupe de la xylazine. La durée de l'anesthésie était plus longue dans le groupe de la romifidine ($\bar{x}$ 20,8, $s_{\bar{x}}$ 2,3 min) que dans le groupe de la xylazine ($\bar{x}$ 15,8, $s_{\bar{x}}$ 1,6 min) alors que l'induction et le réveil étaient excellents dans les deux groupes. La fréquence respiratoire, les résultats des gaz sanguins, le volume des éléments figurés du sang et le niveau des protéines totales ne présentaient pas de différences entre les groupes. Les résultats indiquent qu'une prémédication à la romifidine suivie de diazépam et de kétamine est une méthode satisfaisante d'anesthésie intraveineuse de courte durée chez les chevaux.

(Traduit par docteur André Blouin)

Can Vet J 1996; 37: 601–609

Introduction

An anesthetic technique must possess numerous qualities to be useful as an equine field anesthetic regime (1–3). Ideally it should result in a horse quietly achieving recumbency and quickly reaching a surgical plane of anesthesia. The production of a predictable, consistent duration of anesthesia is desirable, as it will minimize the probability of an abrupt untimely arousal. Adequate muscle relaxation will aid in the assessment of the depth of anesthesia and will provide a visually appealing

Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1.

Address correspondence to Dr. C.L. Kerr.

Requests for reprints should be sent to Dr. W.N. McDonell.

Funding for the project was provided by Boehringer Ingelheim, Canada.

anesthetic, in addition to facilitating the surgery. Recovery should be gradual and allow the horse to smoothly regain a standing position (4). Recumbency itself will place some stress on the hemodynamic and respiratory systems; therefore, the agents utilized should minimize cardiopulmonary insult (5). As trained assistance for the private practitioner is often limited, an optimum regime is one that can be administered via a single injection and will produce a duration of anesthesia adequate for most short surgical or treatment procedures (castration, minor orthopedic), with the capacity to extend the duration of anesthesia using supplemental doses.

The profound calming, muscle relaxation, and analgesic properties of the alpha-2 adrenergic agonist group of drugs (xylazine, detomidine, romifidine) have led to their becoming the standard preanesthetic agents preceding anesthesia with ketamine (6–11). Ketamine acts as a sympathetic stimulant and counteracts some of the vagotonic effects of the alpha-2 agonists, while the alpha-2 agonist drugs minimize some of the muscle hypertonicity associated with the use of ketamine in horses (6). The xylazine followed by ketamine regime is recommended and widely employed for field anesthesia (1,2,12–14). Its relatively consistent anesthetic properties combined with its cardiopulmonary safety have contributed to its popularity (6,15). Muscle relaxation, which on occasion is poor with this regime (6,16,17), can be improved with the inclusion of diazepam in the protocol (2,3,18). Butera *et al* (3) recommended the administration of diazepam, IM, at moderately high doses prior to xylazine and ketamine to improve the quality of anesthesia. Others have included IV diazepam or guaifenesin after xylazine sedation but prior to ketamine (18,19). Although the hemodynamic changes associated with a xylazine followed by diazepam followed by ketamine combination have been reported (18), the study was complicated by the inclusion of halothane in the protocol.

A regime that offers an ease of administration and degree of predictability equivalent to that of xylazine followed by ketamine, but with a longer duration of action, has been sought for several years. Detomidine has not displaced xylazine for use with ketamine, largely because of the diminished recovery scores that are associated with the substitution (17,20). Recumbency time was shown to be prolonged in one investigation with the inclusion of temazepam, a benzodiazepine, to a xylazine followed by ketamine protocol (21). As the authors pointed out, however, no attempt was made to evaluate depth of anesthesia or analgesia during the study, and the reported apparent increase in recumbency time may not represent an increase in useful anesthesia time. Combinations of xylazine or detomidine with tiletamine and zolazepam (a cyclohexamine-benzodiazepine combination) have not shown a consistent quality of anesthesia, when used at recommended doses (17,22,23), and this product has been associated with marked hypoxemia (22,23). Presently, this product is only licensed in the United States for dogs and cats, and it is not approved for use with any species in Canada.

Romifidine is a new alpha-2 adrenoceptor agonist that is commercially available in Europe, Australia, and Canada for sedative use in the horse. Preliminary trials have demonstrated that romifidine produces sedation of similar quality to that produced by xylazine and detomidine, without inducing the same degree of ataxia or head drooping (24). Xylazine remains the shortest acting alpha-2 adrenergic agonist on the market for horses, with romifidine having a dose-dependent duration of effect that approximates that of detomidine.

The purpose of this investigation was to compare the anesthetic characteristics of an anesthetic regime utilizing romifidine followed by diazepam mixed with ketamine (R/D/K) versus a regime using xylazine followed by diazepam mixed with ketamine (X/D/K) in healthy horses subjected to a controlled level of noxious stimuli.

Materials and methods

Animals and instrumentation

Twelve horses, 11 mares and 1 gelding (10 standardbred, 2 Thoroughbred), ranging in age from 4 to 11 y ($\bar{x}$ 6.8 y, $s_{\bar{x}}$ 2.8 y), and weighing between 407 to 504 kg ($\bar{x}$ 473.4 kg, $s_{\bar{x}}$ 26.5 kg) were used in this study. They were all in good health, as determined by physical examination, a complete blood count, arterial blood gas analysis, and a base-apex electrocardiogram. All horses were housed indoors for a minimum of 18 h prior to testing and were fasted for 8 h prior to study. Access to water was provided until the time of the investigation. The experimental protocol was approved by the institutional animal care committee, and the guidelines of the Canadian Council on Animal Care were followed throughout the study.

Instrumentation and baseline measurements took place in standard equine stocks in a temperature-controlled room. Three 22 gauge stainless steel wires were placed sub-dermally using local analgesia (2% lidocaine, Astra Pharma, Mississauga, Ontario). Copper alligator clips were attached to the wires to permit lead I electrocardiograph (ECG) recording with minimal disturbance to the animal. A 20 gauge, 5.1 cm long, catheter (Insyte-W, Deseret Medical, Becton Dickinson, Sandy, Utah, USA) was placed percutaneously in the transverse facial artery using local analgesia (2% lidocaine) and connected to a constant flush pressure transducer system (Spectramed DTX Pressure Transducer System, Spectramed Critical Care Division, Oxnard, California, USA). The ECG and blood pressure were recorded on a 4-channel oscilloscope monitor system (Physio Control VSMI, Physio Control Corporation, Redmond, Washington, USA). The scapulohumeral joint was the zero reference point for blood pressure measurements when the horses were in the standing position, and the manubrium sterni was used as the zero reference point when the horses were in lateral recumbency. The pressure recording system was calibrated using a mercury manometer before and after each experimental period. A jugular vein was catheterized with a 14 gauge, 13.3 cm long catheter (Angiocath, Deseret Medical, Becton Dickinson) to provide IV access for drug administration.

Once a horse achieved recumbency under general anesthesia, a set of stainless steel, 20 gauge needles was placed under the submucosa of the lower lip, 3 cm apart. A second set of needles was similarly placed into the subcutaneous tissue on the lateral aspect of

the uppermost forelimb, 3 cm proximal to the coronary band. The needle hubs served as attachment sites for a constant current, peripheral nerve stimulator (Innervator, Fisher & Raykel Electronics, Auckland, New Zealand).

Experimental protocol

The study was carried out as a blinded, randomized, cross-over trial, with a minimum of 7 d separating the trials. The drug regimes for the 2 trials involved premedication with xylazine (1.1 mg/kg body weight [BW]) (Rompun, Haver, Bayvet Division, Etobicoke, Ontario) or romifidine (100 μg/kg BW) (Sedivet, Boehringer Ingelheim, Burlington, Ontario) given IV, followed by the IV administration of a mixture of diazepam (0.04 mg/kg BW) (Sebex, Boucherville, Quebec) and ketamine (2.2 mg/kg BW) (Ketalean, MTC Pharmaceuticals, Cambridge, Ontario). All persons involved in the experimental and scoring process were blinded to the treatments.

After instrumentation, a stabilization period followed, ranging from 5 to 20 min, depending on the time required for the horse to quieten and achieve an acceptable resting heart rate (HR). Baseline measurements for HR (recorded over 30 s), the presence of arrhythmias (recorded over 30 s); respiratory rate (RR); systolic, diastolic, and mean blood pressures (SBP, DBP, MBP); and rectal temperature were recorded 5 and 10 min prior to the administration of the appropriate premedication agent. Arterial blood gas samples were collected into heparinized syringes (Aspirator, Marquest Medical Products, Englewood, Colorado, USA) from the catheter in the facial artery at both baseline time periods. All arterial blood gas samples were stored on ice and analyzed within 1 h on an automated blood gas analyzer (ABL 5000, Radiometer A/S, Bach-Simpson, Copenhagen, Denmark), which was calibrated with reference serum samples daily and throughout the day with gas samples. Samples were corrected for body temperature. The microhematrocrit method and refractometry were used to determine the packed cell volume (PCV) and total protein (TP) levels, respectively.

Five minutes after the administration of xylazine or romifidine, the measurements were repeated and an arterial blood gas sample was obtained. The horse was then moved a short distance from the stocks to an open area with a rubber flooring. The administration of the diazepam and ketamine mixture took place 10 min after the horses received xylazine or romifidine. Two people assisted in all inductions, which were carried out in identical fashion. One person controlled the head and 1 person held the tail, in case it was necessary to control gross movement of the horse that could prove dangerous to those involved. No attempt was made to control the side to which the horse fell. A 3rd individual video recorded the induction and recoveries to allow future re-evaluation. The quality of the induction was scored by 2 individuals. The scale used (Table 1) was modified from previous studies (11,14).

Induction time was recorded as the time from the administration of diazepam and ketamine (time 0 of anesthesia) until the horse achieved recumbency. Recording of cardiopulmonary and response measurements started at 5 min of anesthesia and were repeated at 5 min intervals until the horse moved into sternal recumbency. The degree of muscle relaxation present was also scored at each time period until the end of anesthesia, using the scale outlined in Table 1.

At each measurement period, after the recording of cardiopulmonary parameters and evaluation of the degree of muscle relaxation, 4 sets of stimuli were applied to the horse to aid in the assessment of depth of anesthesia. The stimuli were applied in a consistent order by the same individual in all cases, with a 10 s interval between each stimulus. The response to each

Table 1. Scoring system for induction characteristics, muscle relaxation, response to stimuli, and recovery characteristics

Score	Induction characteristics
0	Smooth induction, no muscle twitching, no forward or backward movement once the induction agents were administered
1	Smooth induction with no risk of injury to horse or handlers, but horse showed head or limb twitching after induction, or a tendency to walk forward or backward after induction agents were administered
2	Recumbency achieved and the horse remained recumbent; however, the horse fell without relaxation of limbs or with a strong forward or backward movement; possible risk of injury to horse or handler
3	The horse was induced with considerable movement and/or excitement.;the horse may have made subsequent attempts to stand or any other situation that could have resulted in injury to horse or clinician
4	The horse failed to achieve recumbency

Score	Muscle relaxation
0	Muscle relaxation present in trunk and limbs
1	Muscle twitching present in some regions of trunk and limbs
2	Muscle twitching present over the majority of trunk and limbs
3	Muscle rigidity present over the majority of trunk and limbs

Score	Response to stimuli
0	No response
1	Nystagmus created, a blood pressure response or a local muscle response (nerve stimulator) observed
2	Purposeful movement of limbs, head, or neck produced
3	Horse moved into sternal position or stood

Score	Recovery characteristics
0	Stood on first attempt with a clean effort; minimal ataxia observed once standing
1	Stood on first attempt with mild ataxia present once standing
2	Two to 3 attempts made to stand but stood with strong effort on last attempt
3	Several attempts to stand; considerable ataxia present once standing
4	Several weak attempts to stand, may have reassumed recumbency after standing; injuries incurred or had a high probability of occurring

stimulation was scored, based on movement or changes in blood pressure (increase of 5 mmHg or greater in MBP), as outlined in Table 1. Noise stimulation was applied initially with a horn directed into the horse's outer ear. Touch stimuli were performed by slapping the horse once on the rump and once on the flank. Hemostats applied to the pastern and then the shoulder of the non-dependent forelimb for 2 s provided pressure stimuli. Subsequently, an electrical stimulus was utilized to assess the depth of anesthesia, as previously reported (3,6,8,17,22,23). Electrical current is a potent noxious stimulus, similar to that produced by surgical intervention, but with no lasting effect (25). Due to the strength of the electrical stimulus, the less noxious stimuli, which might simulate nonsurgical stimuli in a field setting, were applied first. The peripheral nerve stimulator was attached to the stainless steel needles, first at the lip and then above the coronary band, and a stimulus of 100 Hz was applied for 10 s. A setting of 10 mA was used initially, which was increased 20 mA if a response of less than a 2 was recorded with 10 mA. The response to each stimulation was scored, based on movement or changes in blood pressure (increase of 5 mmHg or greater in MBP), as outlined in Table 1.

A score of 2 or greater in response to any of the stimuli, or the purposeful movement of the horse without the application of a stimulus, was defined as the end of anesthesia. This time was recorded and electrical stimulation was no longer employed. All other stimuli were repeated at the 5 min intervals until the horse achieved sternal recumbency. When the horse stayed in sternal recumbency for longer than 10 min, the touch stimulus (slap) was repeated on the rump at 10 min intervals until the horse stood. The times at which the horse moved into sternal recumbency and subsequently stood were recorded. Recovery, that is the transition from recumbency to standing, took place with 1 person on the lead rope. No attempt was made to control the recovery or to encourage the time of recovery other than with a single slap at 10 min intervals. The recovery was scored by 2 individuals. The recovery scoring system was expanded from scales previously reported (11,14), as outlined in Table 1.

Five minutes after the horse was standing, measurements of HR, frequency of arrhythmias, SBP, DBP, MBP, RR, and rectal temperature were recorded, and an arterial blood gas sample was obtained.

Statistical analysis

Where 2 baseline measurements were obtained, a correlation analysis was carried out prior to the 2 measurements being averaged to give 1 baseline reading. For continuous data measured over time, main effects of treatment and time were evaluated, controlling for animals, with analysis of variance for repeated measures ($P < 0.05$). In analyses that demonstrated a significant main effect, pairwise comparisons were performed between treatments and relative to baseline, using a paired t-test. Bonferonni's method was used to control for the overall level of significance.

Comparisons of the induction time, duration of anesthesia, time to sternal recumbency, and recovery time were analyzed using a two-tailed paired t-test, while the scores for induction, recovery, and muscle relaxation were analyzed using a modified paired t-test analysis ($P < 0.05$). The relative numbers of horses that experienced heart blocks were compared using Wilcoxon's rank-sum test.

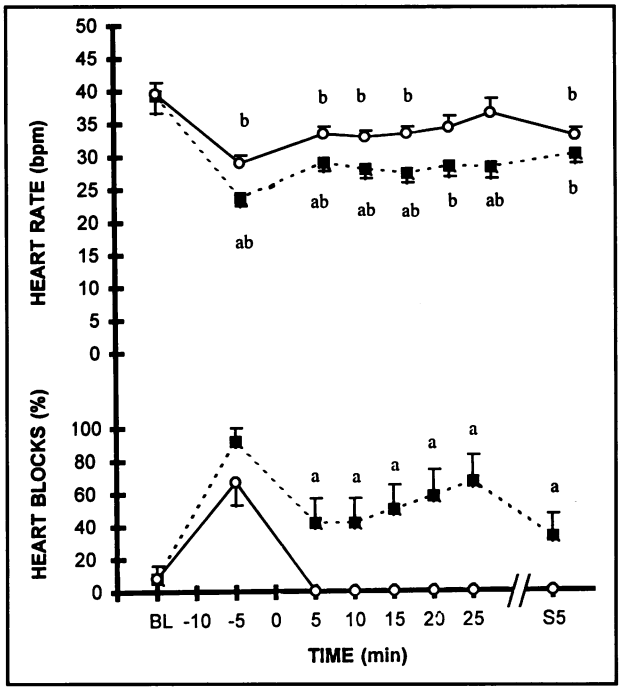

Figure 1. Mean heart rate ($\pm s_{\bar{x}}$) and percent of horses with 2° atrioventricular heart blocks before premedication (baseline, BL), 5 min after premedication with xylazine or romifidine (−5 min), following diazepam/ketamine (5–25 min) and 5 min after standing (S5). Differences ($P < 0.05$) between the romifidine (■) and xylazine (○) treatment groups are illustrated by (a) and differences relative to baseline values within a treatment group are illustrated by (b).

Results

All horses that received romifidine and 11 of the horses that received xylazine were effectively sedated prior to ketamine administration. One high-strung mare showed no clinical signs of sedation from the time of administration of xylazine until the time at which ketamine was scheduled to be administered. The experiment was cancelled and repeated 7 d later, at which time she responded as expected to the premedication and the experiment was completed without complications.

Heart rate was decreased ($P < 0.01$) below baseline values 5 min after sedation and 5, 10, and 15 min after diazepam and ketamine for both treatment groups (Figure 1). In the R/D/K treatment group, HR remained below baseline throughout the remainder of the measurement period. Five min after standing, the HR returned to below baseline values in the X/D/K group. Heart rate was lower ($P < 0.01$) for the R/D/K group at 5 min after romifidine administration and at 5, 10, 15, and 25 min after diazepam and ketamine, when compared with the X/D/K treatment group.

Eleven of the horses in the R/D/K treatment group and 8 horses in the X/D/K treatment group demonstrated 2nd degree atrioventricular heart blocks (2°AVB), 5 min after sedation. In the X/D/K treatment group there were no horses that demonstrated 2°AVB after the administration

Table 2. Cardiovascular and respiratory effects of romifidine (100 µg/kg body weight [BW]) or xylazine (1.1 mg/kg BW) followed by diazepam (0.04 mg/kg BW)[a]

Variable[b]	Treatment[c]	Baseline	5 min after xyl or rom	Time after diazepam/ketamine (min) 5	10	15	20	25	5 min after standing
SBP (mmHg)	R/D/K	155.2 $s_{\bar{x}}$ 4.3	158.7 $s_{\bar{x}}$ 4.5	171.8[e] $s_{\bar{x}}$ 5.4	167.7[e] $s_{\bar{x}}$ 5.9	165.6[e] $s_{\bar{x}}$ 6.3	155.0[e] $s_{\bar{x}}$ 5.7	149.8 $s_{\bar{x}}$ 6.3	128.5[d] $s_{\bar{x}}$ 4.5
	X/D/K	148.5 $s_{\bar{x}}$ 3.7	151.2 $s_{\bar{x}}$ 3.2	138.5 $s_{\bar{x}}$ 4.0	133.8 $s_{\bar{x}}$ 4.4	127.9[d] $s_{\bar{x}}$ 3.9	118.9[d] $s_{\bar{x}}$ 5.3	107.2[d] $s_{\bar{x}}$ 8.7	123.0[d] $s_{\bar{x}}$ 4.2
DBP (mmHg)	R/D/K	98.5 $s_{\bar{x}}$ 2.1	109.6 $s_{\bar{x}}$ 3.2	127.1[d,e] $s_{\bar{x}}$ 5.0	125.3[d,e] $s_{\bar{x}}$ 5.0	119.2[d,e] $s_{\bar{x}}$ 5.7	118.1[d,e] $s_{\bar{x}}$ 4.8	113.3 $s_{\bar{x}}$ 6.0	89.2 $s_{\bar{x}}$ 3.6
	X/D/K	93.8 $s_{\bar{x}}$ 3.0	110.4[d] $s_{\bar{x}}$ 3.9	102.8 $s_{\bar{x}}$ 4.9	99.1 $s_{\bar{x}}$ 5.0	94.1 $s_{\bar{x}}$ 4.3	84.3 $s_{\bar{x}}$ 4.2	77.4 $s_{\bar{x}}$ 5.1	90.5 $s_{\bar{x}}$ 3.4
RR (breaths/ min)	R/D/K	14.6 $s_{\bar{x}}$ 1.5	13.3 $s_{\bar{x}}$ 1.7	12.1 $s_{\bar{x}}$ 2.4	17.8 $s_{\bar{x}}$ 1.6	15.8 $s_{\bar{x}}$ 1.5	16.6 $s_{\bar{x}}$ 1.3	16.5 $s_{\bar{x}}$ 1.2	7.8[d] $s_{\bar{x}}$ 0.5
	X/D/K	14.5 $s_{\bar{x}}$ 1.8	12.4 $s_{\bar{x}}$ 1.2	12.5 $s_{\bar{x}}$ 1.9	14.0 $s_{\bar{x}}$ 1.7	13.3 $s_{\bar{x}}$ 1.4	13.1 $s_{\bar{x}}$ 1.7	15.2 $s_{\bar{x}}$ 2.7	9.9 $s_{\bar{x}}$ 0.8

[a] $\bar{x}$, $s_{\bar{x}}$, n = 12 except at 20 min when n = 11 for R/D/K group, n = 8 for X/D/K group and at 25 min when n = 10 for R/D/K group and n = 5 for X/D/K group
[b] SBP, Systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate
[c] R/D/K, romifidine/diazepam/ketamine; X/D/K, xylazine/diazepam/ketamine
[d] Significantly different from baseline values ($P < 0.05$)
[e] Significantly different from X/D/K treatment group ($P < 0.01$)

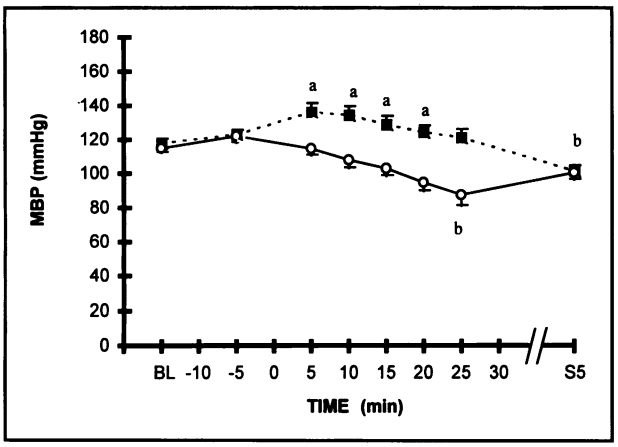

Figure 2. Mean blood pressure (± $s_{\bar{x}}$) before premedication (baseline, BL), 5 min after premedication with xylazine or romidifine (−5), following diazepam/ketamine (5–25), and 5 min after standing (S5). Differences between the romifidine/diazepam/ketamine (■) and xylazine/diazepam/ketamine (O) groups are illustrated by (a) and differences relative to baseline values within a treatment group are illustrated by (b).

of diazepam and ketamine. This was not the case in the R/D/K treatment group and the frequency of 2°AVB was greater from 5 min after the administration of diazepam and ketamine until the end of the measurement period, relative to the X/D/K treatment group (Figure 1).

Systolic, mean, and diastolic arterial blood pressures were higher for the R/D/K group from 5 to 20 min of anesthesia relative to the X/D/K group (Figure 2, Table 2). Systolic pressure was lower than the baseline level for the X/D/K group at 15, 20, and 25 min after diazepam/ketamine. Five minutes after standing, both treatment groups had systolic pressures lower than their baseline measurements. Diastolic arterial blood pressures were higher 5 min after xylazine administration in the X/D/K group, and at 5, 10, 15, and 20 min after diazepam and ketamine in the R/D/K group, relative to baseline values. Mean arterial pressure was lower than baseline values 25 min after diazepam and ketamine in the X/D/K group, and 5 min after standing in the R/D/K group.

Analysis of the respiratory, blood gas parameters, and hematological parameters, which included respiratory rate, arterial pH, oxygen and carbon dioxide partial pressures (PaO_2, $PaCO_2$), bicarbonate (HCO_3), base excess (BE), PCV, and TP, showed no significant differences between groups (Tables 2, 3). Respiratory rate for the R/D/K treatment group was lower than baseline values at the last sampling period, 5 min after the horses were standing. After the onset of anesthesia and recumbency, PaO_2 levels were lower and remained so at all subsequent sampling times for the X/D/K treatment group. In the R/D/K group, the PaO_2 values were lower than baseline levels at all measurements taken with the horse in lateral recumbency, returning to baseline values with the standing postanesthetic sample (Figure 3). There was an increase in $PaCO_2$ above baseline values 5 and 10 min after the administration of diazepam and ketamine in the X/D/K group, and 5 min after diazepam and ketamine for the R/D/K group. Both groups had an increase in $PaCO_2$ at the standing postanesthesia sampling time. Arterial pH paralleled the arterial CO_2 levels with significantly lower levels 5 and 10 min after induction for the X/D/K group, and 5 min after induction for the R/D/K group. Arterial pH increased in the sample taken at 25 min in the X/D/K group but fell below baseline values at the standing sampling time. Arterial plasma bicarbonate rose relative to baseline for the X/D/K group at 5 and 15 min after diazepam/ketamine and 5 min after standing. Base excess was elevated for the latter group 5 min after standing. Arterial TP fell from

Table 3. Respiratory, blood gas, and hematological values after romifidine (100 µg/kg body weight [BW]) or xylazine (1.1 mg/kg BW) followed by diazepam (0.04 mg/kg BW)/ketamine (2.2 mg/kg BW)[a]

			Min after sedation	Min after diazepam/ketamine			Min after standing
Variable[b]	Treatment[c]	Baseline	5	5	15	25	5
pHa	R/D/K	7.44 $s_{\bar{x}}$ 0.01	7.47 $s_{\bar{x}}$ 0.02	7.41[d] $s_{\bar{x}}$ 0.01	7.43 $s_{\bar{x}}$ 0.01	7.44 $s_{\bar{x}}$ 0.01	7.42 $s_{\bar{x}}$ 0.01
	X/D/K	7.44 $s_{\bar{x}}$ 0.01	7.43 $s_{\bar{x}}$ 0.01	7.40[d] $s_{\bar{x}}$ 0.01	7.42[d] $s_{\bar{x}}$ 0.01	7.45 $s_{\bar{x}}$ 0.01	7.41[d] $s_{\bar{x}}$ 0.01
HCO_3 (mmol/L)	R/D/K	28.1 $s_{\bar{x}}$ 0.5	27.4 $s_{\bar{x}}$ 0.5	28.6 $s_{\bar{x}}$ 0.5	28.5 $s_{\bar{x}}$ 0.6	28.8 $s_{\bar{x}}$ 0.6	29.1 $s_{\bar{x}}$ 0.7
	X/D/K	27.6 $s_{\bar{x}}$ 0.6	27.7 $s_{\bar{x}}$ 0.6	28.2[d] $s_{\bar{x}}$ 0.6	28.3[d] $s_{\bar{x}}$ 0.5	28.5 $s_{\bar{x}}$ 0.9	29.3[d] $s_{\bar{x}}$ 0.6
BE (mEq/L)	R/D/K	4.0 $s_{\bar{x}}$ 0.5	3.9 $s_{\bar{x}}$ 0.5	3.8 $s_{\bar{x}}$ 0.5	4.0 $s_{\bar{x}}$ 0.5	4.6 $s_{\bar{x}}$ 0.6	4.4 $s_{\bar{x}}$ 0.7
	X/D/K	3.6 $s_{\bar{x}}$ 0.6	3.5 $s_{\bar{x}}$ 0.6	3.3 $s_{\bar{x}}$ 0.6	3.7 $s_{\bar{x}}$ 0.5	4.5 $s_{\bar{x}}$ 0.9	4.4[d] $s_{\bar{x}}$ 0.6
PCV (%)	R/D/K	33.3 $s_{\bar{x}}$ 1.4	32.8 $s_{\bar{x}}$ 1.2	34.2 $s_{\bar{x}}$ 1.8	33.7 $s_{\bar{x}}$ 1.3	31.7 $s_{\bar{x}}$ 2.3	30.3 $s_{\bar{x}}$ 1.5
	X/D/K	33.3 $s_{\bar{x}}$ 1.7	32.6 $s_{\bar{x}}$ 1.2	31.3 $s_{\bar{x}}$ 0.9	30.5 $s_{\bar{x}}$ 1.1	28.8 $s_{\bar{x}}$ 1.5	29.1 $s_{\bar{x}}$ 0.8
TP (g/L)	R/D/K	67.0 $s_{\bar{x}}$ 1.3	65.6 $s_{\bar{x}}$ 1.5	64.5[d] $s_{\bar{x}}$ 1.4	64.0[d] $s_{\bar{x}}$ 1.4	63.4[d] $s_{\bar{x}}$ 1.3	63.2[d] $s_{\bar{x}}$ 1.4
	X/D/K	67.6 $s_{\bar{x}}$ 1.1	67.5 $s_{\bar{x}}$ 1.2	65.8[d] $s_{\bar{x}}$ 1.3	64.6[d] $s_{\bar{x}}$ 1.4	64.6[d] $s_{\bar{x}}$ 1.3	63.7[d] $s_{\bar{x}}$ 1.2

[a] $\bar{x}$, $s_{\bar{x}}$, n = 12 except at 25 min when n = 10 for (R/D/K group) or n = 5 (X/D/K group)
[b] pHa, arterial pH; HCO_3, arterial bicarbonate concentration; BE, arterial base excess; PCV, packed cell volume; TP, total protein. n = 12 except at 25 min when n = 10 for romifidine and n = 5 for xylazine
[c] R/D/K, romifidine/diazepam/ketamine; X/D/K, xylazine/diazepam/ketamine
[d] Significantly different from baseline ($P < 0.05$)

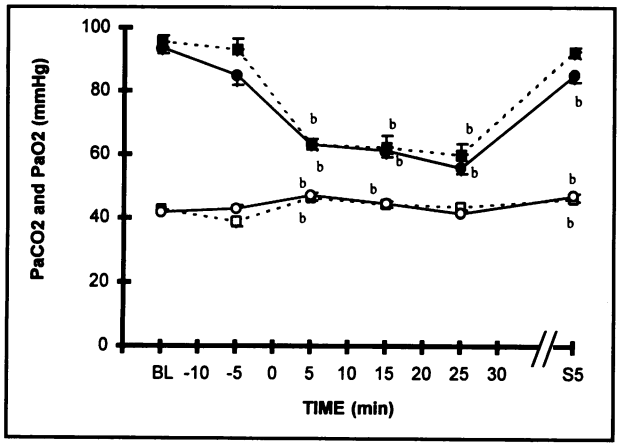

Figure 3. Mean (± $s_{\bar{x}}$) $PaCO_2$ (open symbols) and PaO_2 (closed symbols) levels before premedication (baseline, BL), 5 min after premedication with xylazine or romifidine (−5), following diazepam/ketamine (5–25), and 5 min after standing (S5) from romifidine/diazepam/ketamine (□, ■) and xylazine/diazepam/ketamine (○, ●) anesthesia. Differences ($P < 0.05$) relative to baseline within a treatment group are illustrated by (b); differences between treatment groups were not significant.

baseline values for both treatment groups from 5 min after diazepam and ketamine to the end of the measurement period. There were no differences in PCV relative to baseline values for either treatment group (Table 3).

Analysis of the time from induction to recumbency showed no differences between groups (Table 4). In the R/D/K group, the duration of anesthesia was longer ($P < 0.05$) and varied from 15 min (4 animals) to 40 min (1 animal); 8 of the 12 animals had a duration of anesthesia lasting 20 min or more. In the X/D/K group, the duration of anesthesia lasted from 10 min (4 animals) to 25 min (2 animals); only 4 of 12 animals had a duration of anesthesia lasting 20 min or more. The interval from induction to sternal recumbency and to standing was also longer for the R/D/K group (Table 4). Although always applied last in the series of stimuli, the electrical stimulus defined the end of anesthesia (1st stimulus with score of 2 of greater) in 17 of the 24 experiments. Touch stimulus was the 1st stimulus to which the horse responded with a score of 2 or greater with 3 horses, and pressure stimulus defined the end of anesthesia in 1 experiment. When a horse responded with a score of 2 or greater to any of the first 3 stimuli, an equivalent score was always obtained with the electrical stimulus.

There were no significant differences between groups in scores for induction, recovery, or muscle relaxation during anesthesia (Table 4). All but 1 horse scored a 0 or 1 score on induction, with 1 mare scoring a 2 with the xylazine treatment. All horses showed excellent

Table 4. Characteristics of anesthesia with romifidine (100 µg/kg body weight [BW]) or xylazine (1.1 mg/kg BW) followed by diazepam (0.04 mg/kg BW)/ ketamine (2.2 mg/kg BW)[a]

Treatment[b]	Time to recumbency (sec)	Induction score[c] (0–4)	Time to end-anesthesia (min)	Time to sternal recumbency (min)	Time to standing (min)	Recovery score[c] (0–4)
R/D/K	63.8	0.3	20.8[d]	31.9[d]	44.0[d]	0.3
	$s_{\bar{x}}$ 3.1	$s_{\bar{x}}$ 0.2	$s_{\bar{x}}$ 2.3	$s_{\bar{x}}$ 2.7	$s_{\bar{x}}$ 4.9	$s_{\bar{x}}$ 0.2
X/D/K	54.0	0.4	15.8	25.67	32.2	0.5
	$s_{\bar{x}}$ 2.1	$s_{\bar{x}}$ 0.2	$s_{\bar{x}}$ 1.6	$s_{\bar{x}}$ 1.5	$s_{\bar{x}}$ 3.3	$s_{\bar{x}}$ 0.2

[a] $\bar{x}$, $s_{\bar{x}}$, $n = 12$
[b] R/D/K, romifidine/diazepam/ketamine; X/D/K, xylazine/diazepam/ketamine
[c] See Table 1 for complete explanation of score; induction: 0 = Excellent, 4 = Failure; Recovery: 0 = Excellent, 4 = Failure
[d] Significant difference compared with X/D/K group ($P < 0.05$)

muscle relaxation (score 0) from the time of 1st assessment (5 min) until the end of the period of anesthesia. Scores for recovery were similar to the induction scores with all horses scoring a 0 or 1, except for 1 mare in the X/D/K group, which scored a 2.

Discussion

Quality of anesthesia was excellent with both regimes, as judged by induction characteristics, muscle relaxation, and recovery scores. Hemodynamic and respiratory changes produced by X/D/K and R/D/K were significant but consistent with previous results involving equine induction techniques (6,7,16,22,23).

All alpha-2 agonists produce a decrease in HR in horses at clinically used doses (26). Characteristically, this change is preceded by a transient increase in systemic arterial pressures when these agents are administered IV (7,17,30–32). The temporal occurrence of these events, and prevention of the bradycardia with anticholinergic treatment, implicate baroreceptor activation as the main cause of the observed bradycardia after alpha-2 administration (11,30,32). Peripheral vasoconstriction mediated through alpha-1 and alpha-2 receptors is likely responsible for the increase in systemic blood pressure that is seen immediately after the IV administration of xylazine, detomidine, or romifidine (7,17,30–32). Hypertension with these agents is transient and, typically, blood pressure slowly declines according to the dose and the duration of effect of the particular agent utilized.

In this study, HR fell markedly following sedation with xylazine and romifidine. This bradycardic response was more marked in the R/D/K group, with lower HR and higher systemic arterial pressures during the anesthetic period. Differences among alpha-2 agents in this respect have previously been reported, with detomidine showing greater systemic arterial pressure increases and lowering of HR for a longer time period relative to xylazine when used at clinically equipotent doses (30). Whether or not this is a dose-related phenomenon or a true difference among agents is not yet known. After the administration of diazepam and ketamine, the HR increased to over 25 beats/min in all horses in both treatment groups. A HR of 25 is the minimum rate considered acceptable for the anesthetized horse (2). Ketamine administration is associated with a positive chronotropic effect, primarily due to increased sympathetic drive, and consistently increases HR after alpha-2 sedation (6,7,20). Similarly, systemic arterial pressures are higher with ketamine mixtures, relative to previously utilized barbiturate combinations (15).

Both regimes utilized in this study provided acceptable systemic arterial blood pressures. Horses premedicated with romifidine experienced higher arterial pressures during the anesthetic period relative to the xylazine group. Values for the R/D/K group, however, fell within ranges previously reported for xylazine and ketamine, and below those for detomidine and ketamine when measured by other investigators using similar recording systems (6,7). Differences among agents may be explained by the relative doses and duration of effect, or possibly by intrinsic differences in the agents. Inclusion of diazepam in the anesthetic protocol of this study was unlikely to have influenced the HR changes induced by the alpha-2 agonists (33).

The frequency of atrioventricular arrhythmias increases with the administration of the alpha-2 adrenoceptor agonists (27,28). Similar to the mechanisms resulting in the initiation of bradyarrhythmias, the presence of 2°AVB is attributed to a net increase in vagal tone on the heart. In the present study, more than half of the horses from each treatment group showed 2°AVB after sedation. Horses receiving romifidine had a significantly longer mean duration of heart blocks after diazepam and ketamine were adminstered. Detomidine has been shown to have a longer lasting effect on the cardiovascular system, including the duration of atrioventricular conduction disturbances, when compared with xylazine (30). As romifidine has a duration of action similar to detomidine, it is not unexpected for the duration of the heart blocks to exceed those induced by xylazine.

When placed in lateral recumbency under injectable anesthesia, horses generally show a marked fall in PaO_2 values (6,16,22,23,34) and mild increases in $PaCO_2$ (6,16,23). A combination of intrapulmonary vascular shunting, ventilation-perfusion mismatching, and hypoventilation have been identified as the predominant causes of the reduction in PaO_2 values when inspired oxygen concentration is adequate (5,34). Increasing the inspired oxygen concentration helps to minimize the impact of these factors on the PaO_2. In this study, we

elected not to administer supplemental oxygen to more closely mimic the field situation where oxygen is still not routinely administered. Previous investigators have found that mean PaO_2 values at 5 min after induction with ketamine following xylazine or detomidine sedation range from 49.7 mmHg to more than 70 mmHg (6,8,17). As expected, the horses in this study showed a similar fall in their PaO_2 values, with 3 horses in the X/D/K group and 5 in the R/D/K group demonstrating a PaO_2 of less than 60 mmHg 5 min after the administration of ketamine. By 25 min of recumbency, 5 of the 10 horses in the R/D/K group were in the hypoxic range (<60 mmHg), while all 5 of the horses that were still recumbent in the X/D/K group were hypoxic. Five minutes after standing, PaO_2 values had returned to values approximating baseline values. Ventilation, as reflected by $PaCO_2$ measurements, was depressed at the beginning of the recumbent period and 5 min after standing for both treatment groups. Abdominal tympany in the nonstarved animal may increase the degree of ventilation/perfusion mismatch during anesthesia (4,5), and PaO_2 levels might have been lower if we had not starved the horses before anesthesia.

The quality of anesthesia was excellent with both anesthetic regimes, making both highly suitable for field anesthesia. Previously reported induction and recovery scoring systems have been roughly defined, have contained few classification groups, or were designed for evaluation of widely varying techniques where a large range of characteristics was expected (7,8,17). As we expected high quality inductions and recoveries in the majority of the horses in our study, we attempted to design our classification system carefully, so that more subtle differences among agents could be detected. Under this scoring system, the induction and recoveries uniformly received excellent scores with both regimes, reinforcing the clinical impression that alpha-2 agonist and ketamine based regimes are an improvement on barbiturate based regimes (1,2).

Numerous stimuli have been used in the past and were used in this study to aid in the assessment of the depth of anesthesia (3,6,17,22,23). The peripheral nerve stimulator, as applied, resulted in a consistent response that closely correlated with the clinical impression of depth of anesthesia. The electrical stimulus chosen is quite a strong stimulus and is capable of producing blood pressure elevations in horses during halothane anesthesia (25). Comparing stimuli used in this study is difficult, as they were not applied in random order and the electrical stimulus was not applied after a certain response was obtained, while the other stimuli were continued until the horse achieved sternal recumbency.

With X/D/K, the mean duration from the administration of ketamine until the last stimulus before the horse was responsive was 15.8, $s_{\bar{x}}$ 1.6 min. Unfortunately, comparing the duration of anesthesia among studies is difficult, as many investigators only report the duration of lateral recumbency, or time until standing, and incompletely describe the applied stimuli (6,8,17). Muir *et al* (6) included electrical, pressure, and surgical stimulation to their experimental horses and recorded a mean duration of anesthesia of 16 min (s = 7) with a xylazine and ketamine protocol at the doses utilized in the present study. Wan *et al* (23) reported a mean duration of anesthesia of 13 min (s = 6) using electrical and pressure stimuli with the same anesthetic regime. It thus appears that adding 0.04 mg/kg BW diazepam to the regime does not increase the duration of anesthesia. However, the addition of diazepam does appear to increase the muscle relaxation and overall quality of the anesthesia. In previous reports, 1 of 6 (17) and 1 of 8 (23) horses demonstrated unsatisfactory muscle relaxation during xylazine and ketamine anesthesia. When detomidine was used in place of xylazine with a short time interval between sedation and ketamine administration, the durations of anesthesia (analgesia) and recumbency have been longer, relative to a xylazine and ketamine regime (7). This is not the case when a longer interval between sedation and induction is used (8).

Although the duration of anesthesia was only longer by a mean of 5 min when romifidine was utilized in place of xylazine, this observation was consistent, with all horses having a shorter duration of anesthesia with the X/D/K regime. Moreover, the early failure rate (anesthesia termination at 10 min or earlier), which can be a significant practical problem, is absent with R/D/K (0/12), compared with the fairly high frequency (4/12) seen with X/D/K. The longer duration of anesthesia seen when romifidine was used as the premedication agent in place of xylazine will prove to be useful in the field situation, when it is inconvenient to administer additional agents to prolong recumbency. It is of interest that the duration of anesthesia with R/D/K was not even longer, given the length of action of romifidine (24). The rapid redistribution of ketamine undoubtedly plays a predominant part in the recovery from anesthesia (35). The duration of the effects of xylazine and ketamine can be prolonged for up to at least 30 min with supplemental doses of both drugs (2). We have found that the duration of anesthesia with romifidine and ketamine can be safely extended to 30 min with supplemental doses of ketamine alone, with no adverse effects on recovery (C. Kerr, unpublished observations). It would be advisable to administer supplemental oxygen during such prolonged periods of anesthesia, as is desirable when extending the duration of other IV anesthetic regimes (4,5). To date there is no published experience with incremental or infusion regimes using romifidine beyond 30 min.

Minimal attempt was made to encourage the horses to stand once the point of end-anesthesia was reached. This resulted in long intervals between the end of anesthesia and standing. Clinical experience with the R/D/K anesthetic regime (C. Kerr, W. McDonell, unpublished observations) has shown that with stimulation horses can and will achieve a standing position soon after signs of arousal are present, without a reduction in the quality of recovery. It is also worth noting that our clinical experience using romifidine and ketamine without the incorporation of diazepam in the regime has not been favorable, as too many horses demonstrate muscle rigidity or muscle tremors during recumbency.

We found romifidine provided excellent sedation in horses prior to the administration of diazepam and ketamine. The resulting anesthesia was of excellent quality with inductions and recoveries at least equivalent to those of a X/D/K anesthetic, when performed in an open area resembling a practice situation. The romifidine

premedication resulted in an additional 5 min of anesthesia at a depth at which it is postulated surgery could be ongoing. It also appears the frequeny of unacceptable early recoveries would be reduced if romifidine, instead of xylazine, were used prior to diazepam and ketamine. The hemodynamic changes with R/D/K were similar to those seen with horses receiving X/D/K, with the fall in HR, incidence of 2°AVB, and the increase in systemic arterial pressures being slightly greater. CVJ

References

1. Thurmon JC, Benson GJ. Injectable anesthetics and anesthetic adjuncts. Vet Clin North Am Equine Pract 1987; 3: 15–36.
2. Muir WW. Intravenous anesthetics and anesthetic techniques in horses. In: Muir WW, Hubbell JA, eds. Equine Anesthesia: Monitoring and Emergency Therapy. St. Louis: Mosby Yearbook, 1991: 281–309.
3. Butera TS, Moore JN, Garner HE, Amend JF, Clarke LL, Hatfield DG. Diazepam/xylazine/ketamine combinations for short-term anesthesia in the horse.Vet Med Small Anim Clin 1978; 73: 490–499.
4. Muir WW. Complications: Induction, maintenance, and recovery phases. In: Muir WW, Hubbell JA, eds. Equine Anesthesia: Monitoring and Emergency Therapy. St. Louis: Mosby Yearbook, 1991: 417–443.
5. Schatzmann U, Koehli M, Dudan F, Rohr W, Jones RS. Effect of postural changes on certain circulatory and respiratory values in the horse. Am J Vet Res 1982; 43: 1003–1005.
6. Muir WW, Sharda RT, Milne DW. Evaluation of xylazine and ketamine hydrochloride for anesthesia in horses. J Am Vet Med Assoc 1977; 38: 195–201.
7. Clarke KW, Taylor PM, Watkins SB. Detomidine/ketamine anaesthesia in the horse. Acta Vet Scand 1986; 82: 167–179.
8. Matthews NS, Miller SM, Slater MR, Hartsfield SM, Short CE. A comparison of xylazine-ketamine and detomidine-ketamine anaesthesia in the horse. J Vet Anaesth 1993; 20: 68–72.
9. Szeligowski E, Janicki AM, Krzeski M. Detomidine (Domosedan®) in sedation, premedication and general anaesthesia of horses. Acta Vet Scand 1986; 82: 181–185
10. Short CE, Matthews NS, Harvey R, Tyner CL. Cardiovascular and pulmonary function studies of a new sedative/analgetic (detomidine/dormosedan®) for use alone in horses or as a preanesthetic. Acta Vet Scand 1986; 82: 139–155.
11. Diamond MJ, Young LE, Bartram DH, Gregg AS, *et al.* Clinical evaluation of romifidine/ketamine/halothane anesthesia in horses. Vet Rec 1993; 132: 572–575.
12. Hall LW, Taylor PM. Clinical trial of xylazine with ketamine in equine anaesthesia. Vet Rec 1981; 108: 489–493.
13. Fisher RJ. A field trial of ketamine anaesthesia in the horse. Equine Vet J 1984; 16: 176–179.
14. Watkins SB, Watney GCG, Hall LW, Houlton JEF. A clinical trial of three anaesthetic regimes for the castration of ponies. Vet Rec 1987; 120: 274–276.
15. Brouwer GJ, Hall LW, Kuchel TR. Intravenous anaesthesia in horses after xylazine premedication. Vet Rec 1980; 107: 241–245.
16. Ellis RG, Lowe JE, Schwark WS, Taylor JI. Intravenously administered xylazine and ketamine HCL for anesthesia in horses. J Equine Med Surg 1977; 1: 259–265.
17. Matthews NS, Hartsfield SM, Cornick JL, Williams JD, Beasley A. A comparison of injectable anesthetic combinations in horses. Vet Surg 1991; 20: 268–273.
18. Brock N, Hildebrand SV. A comparison of xylazine-diazepam-ketamine and xylazine-guaifenesin-ketamine in equine anesthesia. Vet Surg 1990; 19: 468–474.
19. 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.
20. Lin HC, Branson KR, Thurmon JC, *et al.* Ketamine, telazol®, xylazine and detomidine. A comparative anesthetic drug combinations study in ponies. Acta Vet Scand 1992; 33: 109–115.
21. Matthews NS, Dollars NS, Young DB, Shawley RV. Prolongation of xylazine/ketamine induced recumbency time with temazepam in horses. Equine Vet J 1991; 23: 8–10.
22. Hubbell JAE, Bednarski RM, Muir WW. Xylazine and tiletamine-zolazepam anesthesia in horses. Am J Vet Res 1989; 50: 737–742.
23. Wan PY, Trim CM, Mueller POE. Xylazine-ketamine and detomidine-tiletamine-zolazepam anesthesia in horses. Vet Surg 1992; 21: 312–318.
24. England GC, Clarke KW, Goossens L. A comparison of the sedative effects of three alpha-2 adrenoceptor agonists (romifidine, detomidine and xylazine) in the horse. J Vet Pharmacol Therap 1992; 15: 194–201.
25. Young SS. Cardiorespiratory responses to electrical stimulation of the buccal mucosa in ponies. Res Vet Sci 1990; 49: 268–274.
26. Clarke KW, Hall LW. "Xylazine" — a new sedative for horses and cattle. Vet Rec 1969; 85: 512–517.
27. Garner HE, Amend JF, Rosborough JP. Effects of BAY VA 1470 on cardiovascular parameters in ponies. Vet Med Small Anim Clin 1971: 1016–1021.
28. Kerr DD, Jones EW, Huggins K, Edwards WC. Sedative and other effects of xylazine given intravenously to horses. Am J Vet Res 1972; 33: 525–532.
29. McCashin FB, Gabel AA. Evaluation of xylazine as a sedative and preanesthetic agent in horses. Am J Vet Res 1975; 36: 1421–1429.
30. Wagner AE, Muir WW, Hinchcliff KW. Cardiovascular effects of xylazine and detomidine in horses. Am J Vet Res 1991; 52: 651–657.
31. Gasthuys F, De Moor A, Parmentier D. Haemodynamic changes during sedation in ponies. Vet Res Comm 1990; 14: 309–327.
32. Sarazan RD, Starke WA, Krause GF, Garner HE. Cardiovascular effects of detomidine, a new alpha-2 adrenoceptor agonist in the conscious pony. J Vet Pharmacol Therap 1989; 12: 378–388.
33. Muir WW, Sams RA, Huffman RH, Noonan JS. Pharmacodynamic and pharmacokinetic properties of diazepam in horses. Am J Vet Res 1982; 43: 1756–1762.
34. Hall LW, Gillespie JR, Tyler WS. Alveolar-arterial oxygen tension differences in anaesthetised horses. Br J Anaesth 1968; 40: 560–568.
35. Waterman AE, Robertson SA, Lowe JG. Pharmacokinetics of intravenously administered ketamine in the horse. Res Vet Sci 1987; 42: 162–166.