Infusion of a combination of propofol and medetomidine for long-term anesthesia in ponies

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Objective—To determine the minimal infusion rate of propofol in combination with medetomidine for long-term anesthesia in ponies and the effects of atipamezole on recovery.

Animals—12 ponies.

Procedure—Ponies were sedated with medetomidine (7 μg/kg of body weight, IV). Ten minutes later, anesthesia was induced with propofol (2 mg/kg, IV). Anesthesia was maintained for 4 hours, using an infusion of medetomidine (3.5 μg/kg per hour, IV) and propofol at a rate sufficient to prevent ponies from moving after electrical stimulation. Arterial blood pressures and blood gas analysis, heart rates, and respiratory rates were monitored. For recovery, 6 ponies were given atipamezole (60 μg/kg, IV). Induction and recovery were scored.

Results—Minimal propofol infusion rates ranged from 0.06 to 0.1 mg/kg per min. Mean arterial blood pressure was stable (range, 74 to 86 mm Hg), and heart rate (34 to 51 beats/min) had minimal variations. Variable breathing patterns were observed. Mean Pa_{O_2} (range, 116 to 146 mm Hg) and mean Pa_{CO_2} (range, 48 to 51 mm Hg) did not change significantly with time, but hypoxemia was evident in some ponies (minimal Pa_{O_2}, 47 mm Hg). Recovery was fast and uneventful with and without atipamezole (completed in 20.2 and 20.9 minutes, respectively).

Conclusions and Clinical Relevance—Infusion of a combination of medetomidine and propofol was suitable for prolonged anesthesia in ponies. Recovery was rapid and uneventful. A combination of propofol and medetomidine may prove suitable for long-term anesthesia in horses. Monitoring of blood gases is essential because of potential hypoxemia. (*Am J Vet Res* 2001;62:500–507)

Propofol, an anesthetic agent administered IV, has become widely used in humans for **total intravenous anesthesia (TIVA)**. Propofol has a number of properties that make it ideal for this purpose. It is short acting and accumulates only slightly. Furthermore, when the maintenance infusion rate is adjusted to the needs of a patient, recovery is rapid, even after prolonged anesthesia. The disadvantages of propofol are that it is a poor analgesic and causes substantial respiratory depression.[1]

Propofol is unsatisfactory as the sole agent for anesthesia in horses, because the volume of drug required is too large to enable sufficiently rapid injection, and the quality of anesthetic induction is unpredictable.[2] However, following sedation with α_2-agonists, propofol administered at doses of 2 mg/kg of body weight results in good-quality induction of anesthesia, and although the volume of drug required is still large and, therefore, expensive, it can be practical. For maintenance of anesthesia during surgery, propofol has been infused at rates of 0.2 to 0.3 mg/kg per min.[a-c] To further reduce the infusion dose of propofol and to improve cardiovascular function, Flaherty et al[3] combined it with an infusion of ketamine hydrochloride. Combined with the analgesic action of detomidine, they achieved a substantial reduction in the dose of propofol and were able to perform castrations with a mean infusion rate of 0.126 mg/kg per min. Because metabolism of ketamine produces norketamine, which is an active metabolite that accumulates,[4,5] prolonged infusion of a combination of propofol and ketamine will result in prolonged or unsatisfactory recovery. Mama et al[6] reported that combined infusion of propofol and xylazine caused profound respiratory depression and exceptionally long recovery times after 75 minutes of anesthesia.

Medetomidine is the most specific and potent α_2-agonist currently available. In dogs and humans, combining it with other anesthetics results in a dramatic decrease of the dose necessary to maintain anesthesia,[7–9] which is reversible with atipamezole.[10]

The hypotheses of the study reported here were that a combination of medetomidine and propofol for maintenance of anesthesia in ponies would require lower doses of propofol than reported by other authors[3,6,a-c] who used other sedatives or analgesics in combination with propofol and that the combination of medetomidine and propofol was suitable for prolonged anesthesia. We also assessed the quality of induction and recovery as well as the effect of atipamezole on recovery.

Materials and Methods

Animals—The study was performed in 12 healthy ponies that ranged from 2 to 24 years old (mean ± SD, 6 ± 5.7 years) and weighed between 157 and 356 kg (mean, 220 ± 56.0 kg). Ponies were fed hay and grass. Twelve hours

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before the start of the experiment, food was removed from the ponies; however, ponies always had access to water.

Instrumentation—A double-lumen, 14-gauge, 150-mm catheter with flow switch[d] was placed in a jugular vein of each pony prior to induction of anesthesia. After induction, the ponies were positioned in left lateral recumbency on a foam-padded mattress. They were immediately intubated, and inspired air was supplemented by oxygen at a flow rate of 2 L/100 kg per min. An ECG was recorded, and an arterial catheter[e] was introduced into the lateral metatarsal artery of the proximal aspect of a rear limb and was attached via a transducer,[f] which had been calibrated level with the heart, to a commercial hemodynamic monitor.[g]

Body temperature was maintained by covering the ponies with a fleece blanket. A heating blanket, positioned under the abdomen of the ponies, was used as necessary.

Anesthetic protocol—Each pony initially was sedated by administration of medetomidine[h] (7 µg/kg, IV). Ten minutes later, anesthesia was induced by administration of propofol[i] (2 mg/kg, IV). Anesthesia was maintained with an infusion of propofol, which commenced immediately after induction, at a rate of 0.15 mg/kg per min. The infusion was administered by using a syringe pump.[j] Dosages were chosen on the basis of data from preliminary trials and published reports.[3,5] The initial infusion rate that was required for the heaviest ponies exceeded the limits of the infusion pump. In these ponies, the calculated dose of propofol was manually injected at 1-minute intervals. The dose rate of propofol was increased by 0.01 mg/kg per min when a purposeful (after stimulation) or spontaneous (nonstimulated) movement was detected. When a pony moved extensively, we increased the depth of anesthesia by administration of a bolus of propofol (0.1 mg/kg); additional boluses were injected at 1-minute intervals until movement ceased. Total dose of propofol administered as a bolus was recorded every 5 minutes. Rate of propofol infusion was decreased by 0.01 mg/kg per min when purposeful movement was not detected within 1 minute of stimulation or when the depth of anesthesia was considered to be too deep, as judged by commonly accepted standards for horses during inhalation anesthesia.[11] The propofol infusion was maintained for 4 hours.

Medetomidine infusion (3.5 µg/kg per h) was started 20 minutes after induction of anesthesia and maintained throughout the anesthetic period. At the end of the anesthetic period, infusion of medetomidine and propofol were discontinued simultaneously.

For recovery, ponies were randomly assigned to 2 groups (n = 6 ponies/group). One group received atipamezole[k] (60 µg/kg, IV), and the other group received an infusion of a sham treatment. Both infusions were given IV 10 minutes after the end of the infusion of medetomidine and propofol or earlier when the pony moved before completion of the 10-minute interval.

Measurement of variables—The quality of induction and recovery was scored (**Appendix**). The ease with which the trachea could be intubated was recorded.

Minimal infusion rate of propofol was determined by application of painful supramaximal electrical stimuli to the coronary band. The area immediately proximal to the coronary band on the forelimb was clipped and prepared aseptically, and two 25-gauge × 1.5-inch acupuncture needles[l] were intradermally inserted 1 cm apart. The needles were attached to a burst stimulator[m] to test analgesia by applying electrical pulses (50 V, 10 milliseconds duration, delivered at 5 Hz for 60 seconds). Each pony received 9 electrical stimulations, with the first electrical stimulation 15 minutes after induction of anesthesia and subsequent stimulations at 25-minute intervals for 4 hours. When a pony did not react to the stimulus with a purposeful movement (as defined by Quasha et al[12]), the infusion rate of propofol was reduced by 0.01 mg/kg per min. When a purposeful movement was evident or when the pony moved spontaneously, boluses of propofol (0.1 mg/kg during a 30-second period) were administered at 1-minute intervals until the pony stopped moving. Then, infusion rate was increased by 0.01 mg/kg per min. Infusion rate of propofol, number of boluses, and amount of propofol were recorded every 5 minutes. These data subsequently were used to calculate the amount of propofol required to maintain adequate depth of anesthesia.

During anesthesia, the following variables were recorded immediately before the application of the supramaximal electrical stimuli used to test analgesia: heart rate, arterial blood pressure, rectal temperature, respiratory rate, and respiratory pattern. Arterial blood samples for blood gas analyses were collected at each time point and analyzed at 37 C, using a blood gas analysis machine.[n]

Variables used to clinically judge depth of anesthesia (position of the eyes, nystagmus, eyelid reflex, blinking, lacrimation, and anal reflex) were recorded. An experienced anesthetist (RB), who was aware of the infusion dose of propofol the pony was receiving, had to predict the response for the applied stimulus, similar to the situation when inhalation anesthetics are used.

The person who assessed quality of recovery was unaware of whether the pony had received atipamezole. During recovery, the following variables were recorded: time of first movement, time of lifting of the head, time to sternal recumbency, time in sternal recumbency, number of attempts to stand, time to standing, and overall recovery score (in accordance with criteria in the appendix).

Statistical analysis—Data were reported as mean ± SD. Hemodynamic data were analyzed by use of an ANOVA for repeated measures. When appropriate, the Scheffe test was used to determine differences between time points. To detect differences in recovery time between the groups with and without atipamezole, the Wilcoxon signed-rank test was used. For all tests, results were considered significant at a value of $P \leq 0.05$.

Results

Induction of anesthesia—Induction of anesthesia with medetomidine-propofol was considered excellent (score of 5) in 7 ponies, good (score of 4) in 3, fair (score of 3) in 1, and bad (score of 2) in 1. Induction was similar in all ponies. When the infusion of propofol started, each pony took several deep breaths and then fell suddenly on its side. Paddling of the limbs ceased in all ponies within 1 minute after becoming laterally recumbent, and all ponies had good relaxation from that point on. In all ponies, tracheal intubation was performed easily following induction; the jaw was relaxed, and laryngeal reflexes were not evident.

Infusion rate of propofol—In all ponies, the initial infusion rate of propofol was 0.15 mg/kg per min. In 7 ponies, the initial infusion rate was reduced by 0.01 to 0.02 mg/kg per min before or immediately after the first stimulation, because these ponies had respiratory rates of < 2 breaths/min. Otherwise, the dose was reduced each time after we did not detect purposeful movement after application of the electrical stimulus.

At infusion rates of 0.06 to 0.09 mg of propofol/kg per min, 5 ponies had spontaneous movement of the head, limbs, or ears at a time that was ≥ 5 minutes

before or after an electrical stimulation. Four other ponies reacted with purposeful movements during applied stimuli when propofol infusion rates were 0.08 to 0.1 mg/kg per min.

Three ponies did not move throughout the anesthetic period (4 hours). At the end of that period, propofol infusion rates were as low as 0.06 mg/kg per min. The overall propofol rates used over time, including injected boluses of propofol, were calculated (**Fig 1**).

Because of movement, 3 ponies needed higher infusion rates than those initially chosen. Six other ponies needed lower doses of propofol with time. When the ponies moved, they often needed several boluses of propofol to achieve a stable plane of anesthesia. Mean amount of each bolus was 0.25 ± 0.19 mg, which corresponded to a dose rate of 0.1 to 0.84 mg/kg. We did not detect apnea in the ponies in association with bolus administration.

Assessment of depth of anesthesia—From the time of induction, the ponies appeared to be in a light plane of anesthesia, with an obvious palpebral reflex, some nystagmus, blinking, and lacrimation. The anesthetist consistently expected a positive response to each electrical stimulus. After each stimulus, all ponies had some autonomically mediated responses such as nystagmus (5 ponies), blinking (5), increase in blood pressure (5), increase in respiratory rate (7), intermittent breathing pattern (4), shivering (2), swallowing (2), and increase in heart rate (1).

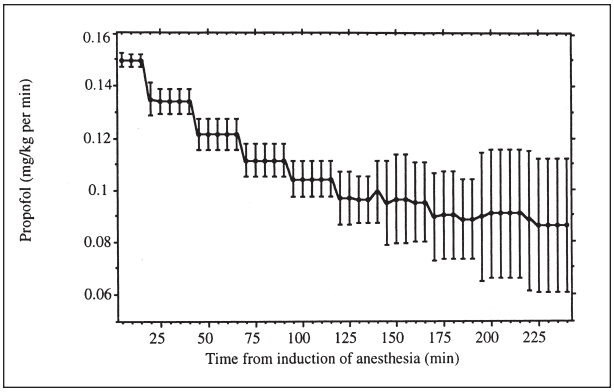

Figure 1—Mean (± SEM) infusion rates for propofol administered in combination with a constant infusion of medetomidine (3.5 μg/kg of body weight per hour) during a 4-hour period in 12 ponies.

All movements, regardless of whether they were spontaneous or in response to an electrical stimulation, were always slow and gentle. All movements were easily controlled by injection of a bolus of propofol followed by an increase (0.01 mg/kg per min) in the infusion rate.

Cardiopulmonary effects —Respiratory rates, pH, and arterial blood gas values were determined (**Table 1**). Two ponies had an intermittent breathing pattern throughout the anesthetic episode. This pattern was characterized by 3 or 4 deep breaths followed by a pause of 20 to 40 seconds. Two other ponies had a similar pattern for the first 25 minutes after induction, and 1 pony had a similar pattern for the first 50 minutes after induction. Five ponies had variable breathing patterns that changed with time. Only 2 ponies had a regular breathing pattern throughout the anesthetic period. Acid-base excess and bicarbonate concentrations increased significantly with time.

Temporal changes in arterial blood pressure and heart rate were detected (**Table 2**); however, values did not change significantly over time, except for diastolic arterial pressure. Values for that variable were significantly lower at 65 and 90 minutes after induction, compared with values 165 minutes after induction.

Other effects—Rectal temperature decreased significantly with time (Table 2). All ponies urinated once or twice during the anesthetic period.

Recovery—Recovery was rapid and uneventful in both groups. Mean time to standing was 20.2 minutes in ponies given atipamezole and 20.9 minutes in ponies without atipamezole. Recovery scores for ponies given atipamezole were 5 (1 pony), 4 (2), and 3 (3), and scores for ponies without atipamezole were 5 (4) and 3 (2). When atipamezole was administered, the number of attempts to stand was 1 (3 ponies), 3 (1), and 4 (2), whereas in ponies without atipamezole, it was 1 (4), 2 (1), and 3 (1). Details of recovery times

Table 1—Respiratory rates (RR), arterial pH, and arterial blood gas values for 12 ponies during 4 hours of anesthesia maintained by use an infusion of medetomidine-propofol

	Time from induction of anesthesia (min)								
Variable	**15**	**40**	**65**	**90**	**115**	**140**	**165**	**190**	**215**
RR (breaths/min)	8.3 ± 3.02 (4–13)	9.8 ± 3.81 (4–15)	8.9 ± 3.73 (4–14)	9.2 ± 3.46 (3–13)	9.0 ± 3.91 (3–14)	9.9 ± 3.94 (4–16)	9.6 ± 4.34 (4–15)	10.3 ± 4.05 (4–16)	11.0 ± 4.66 (4–20)
pH	7.36 ± 0.02 (7.33–7.41)	7.38 ± 0.03 (7.34–7.44)	7.38 ± 0.03 (7.35–7.43)	7.40 ± 0.03 (7.36–7.44)	7.39 ± 0.02 (7.37–7.44)	7.41 ± 0.04 (7.35–7.49)	7.41 ± 0.03 (7.36–7.47)	7.40 ± 0.03 (7.35–7.44)	7.41 ± 0.03 (7.37–7.47)
$PaCO_2$ (mm Hg)	49 ± 3.8 (41–54)	49 ± 3.5 (42–54)	50 ± 3.25 (45–55)	49 ± 3.6 (43–54)	51 ± 4.1 (41–55)	50 ± 6.3 (35–58)	50 ± 5.6 (39–56)	52 ± 4.7 (45–59)	50 ± 6.3 (41–61)
PaO_2 (mm Hg)	146 ± 51.1 (74–219)	134 ± 60.3 (63–244)	134 ± 60.2 (57–241)	128 ± 52.0 (57–235)	117 ± 51.8 (55–221)	125 ± 55.8 (47–229)	123 ± 47.9 (50–208)	125 ± 51.3 (50–234)	123 ± 43.8 (51–218)
HCO_3^- (mmol/L)	27 ± 1.4 (26–29)	28 ± 1.2 (26–30)	29 ± 1.4 (27–31)	30 ± 1.7[a] (25–31)	30 ± 2.0[a,b] (25–32)	30 ± 2.0[a,b] (26–33)	30 ± 2.0[a,b] (27–34)	31 ± 1.5[a,b,c,d] (29–34)	31 ± 2.1[a,b,c] (27–35)
ABE (mmol/L)	2 ± 1.3 (0–4)	3 ± 1.0 (1–4)	4 ± 1.7[a] (2–6)	4 ± 1.3[a] (1–6)	5 ± 1.7[a,b] (1–6)	4 ± 1.4[a,b] (3–7)	5 ± 1.6[a,b,c] (2–8)	6 ± 1[a,b,c,d] (4–7)	6 ± 1.6[a,b,c,d] (2–8)

Values reported are mean ± SEM (range). [a]Mean value differs significantly ($P < 0.05$) from the value at 15 minutes. [b]Mean value differs significantly ($P < 0.05$) from the value at 40 minutes. [c]Mean value differs significantly ($P < 0.05$) from the value at 65 minutes. [d]Mean value differs significantly ($P < 0.05$) from the value at 90 minutes. ABE = Acid-base excess.

Table 2—Rectal temperature, heart rate, and arterial blood pressures for 12 ponies during 4 hours of anesthesia maintained by an infusion of medetomidine-propofol

Variable	Time from induction of anesthesia (min)								
	15	40	65	90	115	140	165	190	215
Rectal temperature (C)	37.1 ± 0.50 (37.7–37.5)	36.5 ± 0.64[a] (35.3–37.2)	36.1 ± 0.75[a] (35–36.9)	36.1 ± 0.59[a] (35–36.8)	36 ± 0.61[a] (35.1–36.8)	35.9 ± 0.65[a] (35–36.7)	35.9 ± 0.65[a] (35.1–36.7)	35.8 ± 0.74[a] (34.8–36.7)	35.7 ± 0.77[a] (34.5–36.7)
Heart rate (beats/min)	40 ± 4.1 (34–48)	41 ± 4.7 (34–50)	42 ± 4.4 (35–51)	41 ± 3.6 (35–49)	41 ± 3.6 (35–49)	41 ± 3.9 (35–48)	40 ± 4.1 (34–48)	39 ± 4.7 (33–48)	40 ± 4.5 (34–48)
SAP (mm Hg)	100 ± 11.3 (85–124)	97 ± 10.66 (82–116)	94 ± 9.48 (79–109)	96 ± 10.13 (78–111)	100 ± 16.58 (82–145)	101 ± 14.15 (90–132)	104 ± 15.15 (90–132)	105 ± 12.01 (94–132)	102 ± 4.63 (91–135)
MAP (mm Hg)	80 ± 6.7 (72–93)	76 ± 9.1 (65–90)	75 ± 9.7 (57–89)	76 ± 8.6 (59–90)	81 ± 13.3 (68–117)	83 ± 10.7 (70–110)	86 ± 10.8 (70–107)	84 ± 10.2 (70–107)	83 ± 8.7 (72–105)
DAP (mm Hg)	66 ± 6.3 (58–78)	63 ± 9.8 (50–78)	60 ± 11.9[b] (43–79)	62 ± 9.4[b] (46–79)	67 ± 13.2 (52–99)	69 ± 11.1 (56–92)	72 ± 9.1 (57–90)	69 ± 9.2 (58–90)	67 ± 8.0 (58–86)

Values reported represent mean ± SEM (range). [a]Mean value differs significantly ($P < 0.05$) from the value at 15 minutes. [b]Mean value differs significantly ($P < 0.05$) from the value at 165 minutes. SAP = Systolic arterial pressure. MAP = Mean arterial pressure. DAP = Diastolic arterial pressure.

Table 3—Interval from termination of infusion until various events during recovery and scores awarded for quality of recovery in 12 ponies following 4 hours of anesthesia maintained by an infusion of medetomidine-propofol

Variable	Group*	
	Atipamezole (n = 6)	Sham-treated (n = 6)
Movement (min)	9.2 ± 3.22 (5.6–12.5)	6.2 ± 4.16 (1.7–12.48)
Lifting of the head (min)	9.4 ± 3.24 (5.6–12.85)	10.9 ± 4.05 (5.9–15.9)
Attained sternal recumbency (min)	9.8 ± 2.86 (6.5–12.9)	11.2 ± 4.42 (5.9–16)
Duration of sternal recumbency (min)	6.5 ± 8.95 (0–24.1)	9.1 ± 7.42 (13–21.5)
First attempt to stand (min)	15.7 ± 10.42 (7.2–35.5)	20.1 ± 10.08 (11.8–37.5)
Standing (min)	20.2 ± 10.09 (8.5–35.6)	20.9 ± 9.68 (21.1–37.5)
No. of attempts to stand	2.3 ± 1.51 (1–4)	1.5 ± 0.14 (1–3)
Recovery score†	3.7 ± 0.82 (3–5)	4.3 ± 1.03 (3–5)

Values reported are mean ± SEM (range).
*Six ponies received atipamezole (60 μg/kg of body weight, IV) 10 minutes after the end of the infusion or when the pony first moved; 6 ponies received a sham treatment. †Scale of 1 to 5, with 1 being very poor and 5 being excellent.
See Appendix for scoring criteria.

and scores were recorded (**Table 3**). Values did not differ significantly between the groups.

Discussion

Minimal infusion rate is a standard measure for injectable anesthetics that has been used to allow comparison of the cardiopulmonary effects produced by equipotent doses of various agents. The term minimal infusion rate was first defined by Sear et al[13-17] as the rate of infusion that would barely suppress movement in response to surgical stimulation. Although not used in the definition for humans, any movement in response to surgical stimulation of the abdomen or thorax is considered to be purposeful.[o] Thus, minimal infusion rate can be compared to Minimum alveolar concentration (MAC), a similar standard that is used to define the potency of inhalation anesthetic agents. However, although minimal infusion rate and MAC are measured in a similar manner, they may not always be comparable. The concentration of inhalation anesthetic agent in the blood closely parallels that in the alveoli and can be altered repeatable and predictably, and it is possible to obtain breath-by-breath measurements of end tidal concentration of agent. In contrast, the blood concentration of an injectable agent, which requires laboratory methods for measurement, will depend on the total dose injected and the pharmacokinetics that govern redistribution and elimination of the agent. Thus, unlike MAC, minimal infusion rate may be a time-dependent variable.[17] The approach currently used in humans is to determine target plasma concentrations of propofol. These are **blood concentrations that prevent a positive response to a surgical stimulus in 50% of a patient population (CP_{50})**.[18] Such target concentrations then are used in combination with pharmacokinetic data of propofol to program infusion pumps for controlled infusion anesthesia. However, target concentrations and pharmacokinetics are dependent on many factors such as patient age, type of surgery, concurrent use of other drugs, hemodynamics, sensitivity of certain patients to the drug, and ability of the drug to reach the target site.[19] It would prove difficult to determine the CP_{50} in horses for medetomidine-propofol infusions, because it is not possible to obtain instantaneous measurement of blood concentrations of the drugs, and knowledge of the pharmacokinetics of these drugs in this species is currently inadequate to enable accurate prediction.[5] Thus, we chose to determine minimal infusion rate as a practical approach to TIVA.

The study reported here revealed some of the problems encountered when determining minimal infusion rate in horses. These problems included technical difficulty when infusing sufficient amounts of propofol to large animals (even though all were ponies), potential that there would be an accumulation of propofol with time, difficulty in anticipating the

response to stimulation, and the fact that some ponies had spontaneous movement not associated with such stimulation.

For this study, we cannot be certain whether propofol accumulated as a result of the high infusion rates used initially or as a result of the prolonged nature of the study. Apart from the 7 ponies in which infusion rates of propofol were adjusted in response to respiratory depression at the beginning of anesthesia, infusion rates were changed only every 25 minutes, as determined by the response to applied stimuli. Certain ponies required variable doses of propofol to prevent positive responses, and, therefore, it is difficult to determine whether some ponies were consistently given a higher dose than necessary. Three ponies did not respond to stimulation and did not spontaneously move throughout the anesthetic period, at the end of which they were receiving propofol at the rate of 0.06 mg/kg per min. It is possible that these ponies also would not have moved if 0.06 mg/kg per min had been used as the initial infusion rate, rather than 0.15 mg/kg per min. Additional studies are required to elucidate the plasma propofol concentration at which responses are detectable.

The infusion dose of propofol chosen for the initial rate in this study proved to be too high, but it was considered appropriate, because it was the lowest propofol infusion dose successfully used in ponies and horses. Investigators in most other studies have used considerably higher doses.[3,20,a-c] Nolan et al,[5] after medicating horses with detomidine and inducing them with ketamine, injecting an initial bolus of propofol (0.5 mg/kg), and administering a constant infusion of ketamine, determined that propofol be infused at the rate of 0.15 mg/kg per min. Mama et al[6] infused propofol at a constant rate of 0.15 mg/kg per min for 75 minutes in combination with constant infusion of xylazine, and 3 of 6 horses moved at least once in response to noxious stimuli. Other authors, although they also combined propofol with other drugs such as guaifenesin or α_2-adrenoceptor agonists, used higher infusion rates (0.2 to 0.4 mg/kg per min).[3,20,a-c]

In the study reported here, none of the ponies moved when propofol was infused at rates of > 0.1 mg/kg per min; however, despite this, all ponies had some autonomic responses to each electrical stimulus. Such responses included an increase in arterial blood pressure or respiratory rate, blinking, nystagmus, or lacrimation. On the basis of experiences with horses anesthetized with inhalation anesthetics,[11] the anesthetist predicting the outcome consistently anticipated a positive response to stimulation, but such responses were not evident. Other authors who have used propofol combined with sedatives or analgesics in equidae[21,22] have commented similarly on detection of signs that, when seen in horses under the influence of volatile agents, would indicate that the depth of anesthesia was inadequate. To avoid administration of an overdose of propofol in patients, it is imperative that the anesthetist be aware of this difference in the signs of depth of anesthesia with medetomidine-propofol. The anesthetist initially should try to choose an anesthetic depth that allows some horses to respond with movements to surgical stimuli at the time they initiate infusion of propofol. Because movements in response to painful stimuli were always gentle and easy to control, this should be a relatively safe method for horses and anesthetic personnel when learning to use medetomidine-propofol in patients, without risking overdoses.

Difficulty in judging the depth of anesthesia by use of classic signs may explain the much higher doses of propofol that have been used previously. Investigators that have used propofol infusions when performing surgery in horses have not judged depth of anesthesia by allowing purposeful movements in response to stimulation.[a,c] Only Flaherty et al[3] reported that 2 of 4 horses given propofol (mean infusion rate, 0.33 mg/kg per min) for 74.3 minutes had movement in response to surgical stimulation. The authors of that study[3] used detomidine as a sedative and ketamine as an induction agent, both of which certainly reduced the minimal infusion rate of propofol. Use of medetomidine infusion in the study reported here reduced the amount of propofol needed to maintain anesthesia by 30 to 60%, compared with concentrations used in other studies. In the ponies that had spontaneous movement despite lack of stimulation, medetomidine provided analgesia such that hypnosis became the limiting factor in the maintenance of anesthesia. Analgesic properties of medetomidine at the rate used in this study were more potent in reducing the amount of propofol needed for maintenance of anesthesia, compared with results for xylazine.[6] Only when propofol has been combined with a constant infusion of ketamine have dose reductions been achieved comparable to those achieved with medetomidine.[3] Contrary to medetomidine, ketamine infusions can only be used safely for a limited period, because the metabolite norketamine accumulates. Norketamine possesses hallucinatory properties[23] and is redistributed and eliminated much slower than ketamine.[5] Recovery after propofol-ketamine would probably become worse with increasing duration of anesthesia. In dogs, medetomidine has a dose-dependent effect on minimal infusion rate of propofol.[7] It has not yet been determined whether there is a similar effect in horses and whether it has an effect on cardiopulmonary function.

Anesthetic induction in the study reported here was extremely sudden and differed from the smooth anesthetic inductions usually seen with ketamine in which horses slowly assume sternal recumbency and then lateral recumbency.[24] As a result of this, for some horses (eg, horses with fractures that cannot be stabilized prior to induction), the use of propofol as an induction agent cannot be recommended. Endotracheal intubation, on the other hand, was always easily accomplished with propofol, a fact that also has been reported in human anesthesia.[25] There was a high incidence of paddling of the forelimbs immediately after induction in our study. This has been reported by other authors who used propofol for induction in unsedated horses.[2] Nolan[21] reported fair anesthetic induction in ponies following sedation with detomidine (21 μg/kg), but Aguiar et al,[22] who administered agents to 6 horses in accordance with the same regimen, and Mama et al,[6] who used xylazine for sedation,

reported only good inductions. The use of a higher dose of medetomidine carries the risk of a horse becoming recumbent,[26] and, therefore, it cannot be recommended. In large horses, the use of agents for anesthetic induction in accordance with an alternative regimen may be appropriate.

Heart rate and arterial blood pressure were remarkably stable throughout the anesthetic period. They remained within commonly accepted limits, but an exact measurement of cardiovascular function will only be possible during more detailed studies.

Respiratory pattern was variable during propofol-induced anesthesia. This has been reported with ketamine[27,28] and, infrequently, with propofol.[3,29] The cause remains unknown. When blood gas analysis is available to assess arterial oxygenation, it may not be of clinical importance. Without facilities for blood gas analysis, assessing the adequacy of respiration may be more difficult than when inhalation anesthetics are used. In the authors' experience, a change in respiratory pattern during inhalation anesthesia aids in assessment of depth of anesthesia. However, the irregular breathing patterns that were evident during infusion of propofol may complicate assessment of anesthetic depth in clinical practice.

Propofol causes dose-dependent respiratory depression in humans,[1] dogs, cats,[30] and horses.[3,5,6] In contrast to reports of other authors who used propofol infusions in horses,[3,6] Pa_{CO_2} in the 12 ponies of our report were stable and within reference ranges for anesthetized horses. Mama et al[6] reported extreme mean values for Pa_{CO_2} as high as 103 mm Hg, and Flaherty et al[3] reported a horse with a Pa_{CO_2} of 16 kPa. The lack of pronounced hypoventilation when agents were administered in accordance with the infusion regimen in our study also supports the hypothesis that the infusion rates were close to minimal infusion rate and that they minimized respiratory depression. In dogs, administration of medetomidine before propofol-induced anesthesia caused greater respiratory depression than use of xylazine or situations in which other medications were not used.[31] However, those authors used the same dose of propofol in all groups, probably resulting in an excess of propofol in the medetomidine-medicated group.

Although mean arterial oxygen tensions were maintained at values expected only with oxygen supplementation, some ponies had severe hypoxemia throughout anesthesia. Hypoxemia is a common problem when propofol is used in horses[6,21,22,p] and dogs.[32] The influence of medetomidine in our ponies was unknown, but in dogs, differing doses of medetomidine before identical propofol infusion did not have significant effects on arterial oxygen tensions.[33-35] Steffey et al[36] described large variations in Pa_{O_2} values in certain horses during inhalation anesthesia in which they had spontaneous respiration and were breathing pure oxygen. Because inspired oxygen concentrations and Pa_{CO_2} values were stable, the authors speculated that the major reason for the observed changes were related to venous admixture, and should this prove to be true, the problem may be accentuated in larger horses. More detailed studies of cardiovascular function during anesthesia induced by infusion of medetomidine-propofol should help to further elucidate the cause of the hypoxemia detected in the study reported here.

Blood pH, acid-base excess, and bicarbonate concentration increased significantly with time. However, these values were all still within reference ranges after 4 hours of anesthesia. It is interesting, because an increase in Pa_{CO_2} usually causes respiratory acidosis during anesthesia of horses. Medetomidine infusion does not cause this phenomenon.[35] A possible explanation is that the lipids contained in the propofol formulation induced a trend toward metabolic alkalosis. In contrast, in children that were infused with propofol over several days, hyperlipidemia developed together with metabolic acidosis.[37] However, those children had other diseases such as pneumonia and liver failure that could have influenced acid-base balance and may explain the difference from results of the study in horses reported here.

Prior to our study, the greatest duration for propofol infusions in horses was 2 hours.[20] In that study, the investigator infused propofol at a constant rate of 0.25 mg/kg per min, and the ponies stood up calmly within 21 to 29 minutes after the end of infusion. Recovery times in the study reported here after 4 hours of anesthesia were rapid (21.2 and 21.9 minutes, respectively, for ponies with and without atipamezole), uneventful, and were within similar ranges reported after infusion for 2 hours.[20] In humans, the **context-sensitive half-life (CRT)**, which is the time after propofol infusion in which the blood concentration of propofol is halved,[38] is short even after prolonged infusions.[1] The CRT for infusions up to 3-hours duration is < 25 minutes. In ponies, the CRT after an infusion of 1-hour duration is even shorter (ie, 5.8 minutes).[5] Because propofol blood concentration has to decline only by 10 to 21% to permit awakening, when titrated to effect, recovery is rapid even after prolonged infusions, as reported here. Authors have reported prolonged recovery periods of 80 minutes[6] after propofol was infused for only 75 minutes, which was probably related to the use of a relatively high dose of propofol.

Recovery was similar, regardless of whether atipamezole was administered. Because the IV administration of atipamezole carries a risk of severe hypotension,[q] clinicians should carefully select situations for its use.

In the study reported here, rectal temperature decreased significantly with time, despite measures to maintain temperature throughout the anesthetic period. Medetomidine in dogs and cats is commonly associated with a decrease in body temperature.[39] Body temperature affects anesthesia. The MAC decreases in a linear manner in response to a reduction in body temperature.[40] Thus, minimal infusion rate of propofol also may be decreased. It is likely that rectal temperature does not always indicate core body temperature, and the effect of temperature on minimal infusion rate warrants further investigation.

The administration of α_2-adrenoceptor agonists causes inhibition of antidiuretic hormone, antagonism of renal tubular action, and an increase in glomerular filtration, thus leading to increased urine output.[41]

Medetomidine causes a dose-dependent increase in urine output.[42] Although we did not quantify the amount of urine produced in the horses of our study, subjectively, it seemed to be remarkable. The ponies all urinated during anesthesia. In patients, it may be necessary to catheterize the bladder, because increased urine output will lead to bladder distention and potential contamination of the surgical and recovery areas.

[a]Hartsfield SM, Matthews NS, Taylor TS, et al. Detomidine-propofol anesthesia for carotid artery translocation in donkeys (abstr). *Vet Surg* 1994;23:75–76.

[b]Matthews NS, Chaffin NK, Hartsfield SM, et al. Propofol for immobilization of neonatal foals (abstr). *Vet Surg* 1994;23:76.

[c]Taylor PM, Fowden AL, Bloomfield MR. Propofol anesthesia for surgery in late gestation pony mares (abstr), in *Proceedings*. 6th Int Conf Vet Anaesthesiol 1997:123.

[d]Hydrocath, Ohmeda, Hatfield, UK.

[e]Angiocath, Beckton and Dickinson UK, Oxford, UK.

[f]T-150-AD, Viggo-Spectramed, Swindon, UK.

[g]Kolormon, Kontron Ltd, Watford, UK.

[h]Domitor, Orion Corp, Turku, Finland.

[i]Rapinovet, Malinckrodt, Vericoe Marlow, UK.

[j]P4000, IVAC, Basingstoke, UK.

[k]Antisedan, Orion Corp, Turku, Finland.

[l]Taki acupuncture needle, MFG Co, Anyang, Korea.

[m]S48 grass stimulator, Grass Co, Mass.

[n]ABL5, Radiometer, Copenhagen, Denmark.

[o]Sear JW, University of Oxford, Dept of Anesthesiology, Oxford, UK: Personal communication, May 2000.

[p]Pablo J, Bailey J, Nicklin C. Evaluation of guaifenesin-propofol and sevoflurane in premedicated horses, in *Proceedings*. 6th Int Conf Vet Anaesthesiol 1997;123.

Appendix

Criteria used to assess quality of induction and recovery

Induction (score 1 to 5)
- 1 = very poor, horse fell unpredictably, risk of injury to horse
- 2 = poor, horse attained recumbency unpredictably, but risk of injury to horse was minimal
- 3 = fair, horse slowly attained sternal or lateral recumbency, noticeable paddling of limbs or shaking of head
- 4 = good, horse slowly attained recumbency, only slight paddling of limbs or shaking of head
- 5 = excellent, horse attained recumbency slowly and smoothly, no paddling or head shaking

Recovery (score of 1 to 5)
- 1 = very poor, bad recovery with high risk of injury
- 2 = poor, horse made > 1 attempt to stand and was excited
- 3 = fair, horse made > 1 attempt to stand but was calm
- 4 = good, horse stood on first attempt but had some ataxia
- 5 = excellent, horse stood on first attempt and had minimal or no ataxia

[q]Antisedan product insert, Pfizer, London, UK.

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