Effects of acetylcholinesterase inhibition on quality of recovery from isoflurane-induced anesthesia in horses

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Objective—To compare effects of 2 acetylcholinesterase inhibitors on recovery quality of horses anesthetized with isoflurane.

Animals—6 horses in phase 1, 7 horses in phase 2A, and 14 horses in phase 2B.

Procedures—The study comprised 3 phases (2 randomized, blinded crossover phases in horses undergoing orthopedic procedures and 1 prospective dose-determining phase). In phase 1, horses were anesthetized with isoflurane and received neostigmine or saline (0.9% NaCl) solution prior to anesthetic recovery. Phase 2A was a physostigmine dose-determining phase. In phase 2B, horses were anesthetized with isoflurane and received neostigmine or physostigmine prior to recovery. Objective recovery events were recorded and subjective visual analogue scale scores of recovery quality were assigned from video recordings.

Results—Recovery measures in phase 1 were not different between horses receiving neostigmine or saline solution. In phase 2A, 0.04 mg of physostigmine/kg was the highest cumulative dose that did not cause clinically relevant adverse behavioral or gastrointestinal effects. Horses receiving physostigmine had higher mean ± SD visual analogue scale recovery scores (70.8 ± 13.3 mm) than did horses receiving neostigmine (62.4 ± 12.8 mm) in phase 2B, with fewer attempts until sternal and standing recovery. Incidence of colic behavior did not differ among groups.

Conclusions and Clinical Relevance—Inhibition with physostigmine improved anesthetic recovery quality in horses anesthetized with isoflurane, compared with recovery quality for horses receiving neostigmine. Inhibition of central muscarinic receptors by inhalation anesthetics may underlie emergence delirium in horses recovering from anesthesia. (Am J Vet Res 2014;75:223–230)

Abbreviations

CAS Central anticholinergic syndrome
M1 Muscarinic subtype 1 receptor
VAS Visual analogue scale

Anesthesia of equine species continues to be associated with a high proportion of fatalities (between 0.24% and 1.8%), with a presumably even higher incidence of nonfatal perianesthetic morbidity.1–3 At least one-third of perioperative fatalities are attributable to complications during recovery.2 A substantial quantity of an inhaled anesthetic is still present in horses during attempts to stand after discontinuation of anesthesia and may be sufficient to adversely affect neurologic and motor function.4 This likely affects overall recovery quality from inhalation anesthesia, which can vary from calm and smooth to violent, frantic, and uncoordinated, predisposing to injury. Emergence delirium may be exacerbated in certain horse breeds as a result of prolonged anesthesia or painful surgical procedures and might be ameliorated by postanesthetic administration of sedatives.5

Emergence delirium in horses behaviorally mimics CAS in some pediatric and adult humans in which individuals awaken from inhalation anesthesia in a dysphoric, excitable, and inconsolable state. Central anticholinergic syndrome is caused by inhibition of muscarinic acetylcholine receptors within the brain, thereby creating a highly excitable state.6,7 The incidence of CAS is between 5% and 18% of human anesthesia patients, depending on age and anesthetic technique.8,9 The M1 and nicotinic acetylcholine receptors play an important role in cognitive function, arousal and consciousness, learning, and memory.10,11 Anesthetic drugs that interfere with release of acetylcholine from presynaptic nerve terminals or drugs that block the postsynaptic M1 are capable of causing cognitive impairments postoperatively that could contribute to postanesthetic delirium manifesting as an inconsolable state during
the return to consciousness. Among their many cell receptor interactions, inhalation anesthetics inhibit both nicotinic acetylcholine receptors and muscarinic acetylcholine receptors, even at concentrations below the minimum alveolar concentration; thus, they have the potential to precipitate CAS.

Physostigmine, a tertiary amine acetylcholinesterase inhibitor with good penetration of the blood-brain barrier, is used to treat CAS in humans. Neostigmine, a quaternary amine that does not readily cross the blood-brain barrier unless the barrier integrity is disturbed, is used less frequently than physostigmine to treat CAS in humans but with occasional success. Neostigmine has been administered in horses to reverse neuromuscular blockade and to treat large intestinal ileus. Physostigmine has been used historically in horses for the treatment of neuromuscular diseases such as spasmodic myalgia and myositis. To our knowledge, acetylcholinesterase inhibitors have not been evaluated for their use in the treatment of CAS or prevention of emergence delirium in horses following inhalation anesthesia.

The peripheral effects of acetylcholinesterase inhibitors are clinically obvious, particularly increases in gastrointestinal motility and defecation. These clinical signs make it impossible to conduct a blinded study to compare treatment with physostigmine and a control solution. Thus, the study reported here was conducted in 2 phases. Phase 1 was designed to test whether neostigmine, an acetylcholinesterase inhibitor that does not substantially penetrate the blood-brain barrier in healthy animals, would have effects similar to those of a control solution. There were 2 objectives for phase 2. In phase 2A, we intended to determine the physostigmine dose that would not cause spasmodic colic in a small group of awake horses. In phase 2B, we tested the hypothesis that administration of a single dose of physostigmine (an acetylcholinesterase inhibitor with central and peripheral effects) would be associated with improved subjective postanesthetic recovery scores and fewer adverse postanesthetic events in horses receiving isoflurane, compared with results for isoflurane-anesthetized horses receiving a dose of neostigmine that has been used to safely reverse neuromuscular blockade in horses. Preliminary experiments confirmed that the peripheral effects of physostigmine were similar to those described for neostigmine, which ensured that the investigators performing the subjective recovery evaluations could remain blinded as to the treatments administered.

Materials and Methods

Animals—Three groups of horses were used for the 2 phases of the study. Six horses were used in phase 1, 7 horses were used in phase 2A, and 14 horses were used in phase 2B. All horses were healthy as determined on the basis of physical examination and measurement of PCV and total protein concentration. Experiments were approved by the Institutional Animal Care and Use Committee of the University of California-Davis.

Phase 1 (neostigmine vs a control solution)—Six horses (2 Morgans, 2 Holsteiners, 1 Saddlebred, and 1 Paint) were enrolled in phase 1. Horses were anesthetized 2 times (interval between anesthetic episodes, 3 weeks) for surgeries to correct bilateral mandibular core defects as part of an unpublished study conducted to investigate bone healing. The same surgery was performed by the same surgeons during both anesthetic episodes.

A blinded, randomized, prospective crossover design was used for phase 1. Food was withheld from horses for 12 hours prior to the experiment; water was available ad libitum. On the morning of a surgery, a catheter was aseptically placed in a jugular vein of a horse, and the horse’s mouth was rinsed with water. Horses were administered phenylbutazone (1 mg/kg, PO) and sedated with xylazine hydrochloride (1 mg/kg, IV) followed by morphone sulfate (0.1 mg/kg, IV). Anesthesia was induced with ketamine hydrochloride (2 mg/kg, IV). Horses were orotracheally intubated and connected to a large animal anesthesia machine. Anesthesia was maintained for 3 hours by the administration of isoflurane (end-tidal concentration, 1.57%; as measured with a calibrated infrared gas analyzer). Horses were positioned in dorsal recumbency on a water bed with the limbs supported and were mechanically ventilated throughout anesthesia to maintain 

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the endotracheal tube still in place. Oxygen (15 L/min) was insufflated through a hose positioned such that the end of the hose was located two-thirds of the way down the orotracheal tube. The orotracheal tube was removed when a horse was able to stand. Once horses were able to ambulate, they were returned to their stalls and immediately offered a moist bran mash.

Events for assessment of recovery quality were measured from the time of discontinuation of anesthesia and included interval to first movement, first head lift, first swallow, first return to sternal recumbency, first attempt to stand, standing (recovery), and extubation; total anesthetic time (anesthetic induction to discontinuation of anesthesia) was also recorded. Objective data collected included the number of times a horse lifted its head but was unable to maintain it so the head fell back down against the floor, number of attempts to achieve sternal recumbency, and number of attempts to stand.

Two investigators (AJW and LSB) who were unaware of the treatment administered to each horse separately reviewed and scored the quality of anesthetic recovery for each horse. Categorical data included the frequency of urination, defecation, or bloating during the recovery period and the severity (judged as none, mild, moderate, or severe) of excitement, ataxia, muscle fasciculations, and injury observed during recovery. Both observers used a VAS (a 100-mm horizontal line with 0 mm indicating the worst recovery possible and 100 mm indicating the best recovery possible) to provide a subjective assessment of recovery quality.

One investigator (AJW) who was not aware of the treatment administered to each horse auscultated gastrointestinal tract sounds (auscultation of 4 abdominal quadrants) of the horses. Auscultations were performed before anesthesia, at the time of standing during anesthetic recovery, and hourly for 3 hours after a horse was able to stand. Gastrointestinal motility scores were assigned as increased, decreased or absent, or unchanged, compared with preanesthetic intestinal activity.

Horses were assessed for behavioral signs of colic (looking at the flank, pacing in the stall, kicking at the abdomen, pawing at the ground, or rolling) before anesthesia, at the time of anesthetic recovery (horse able to stand), and hourly for 3 hours after recovery. Horses with signs of colic that warranted treatment with analgesics underwent a full diagnostic evaluation for colic, which was performed by an equine surgeon. Horses with signs of pain attributable to the surgical procedures or colic were treated with analgesics (an opioid, an α2-receptor agonist, or both) as determined by the primary surgeon. Horses were removed from further colic assessments if analgesics were administered during the postoperative period.

Phase 2A (physostigmine dose-determining experiment)—Four Quarter Horses were used initially to determine the highest dose of physostigmine that did not evoke signs of abdominal discomfort or excitement. Food was withheld from all horses for 12 hours prior to the experiment; water was available ad libitum. Horses were anesthetized twice (interval between anesthetic episodes, ≥ 3 weeks) for surgeries that were part of 2 other studies (an unpublished mandibular core defect study or a study of perfusion of the distal aspect of both forelimbs). For each horse, the same surgery was performed by the same surgeons during both anesthetic episodes.

Anesthesia and anesthetic procedures were identical to those for phase 1. Each horse received IV infusions of physostigmine (0.04 mg/kg) or neostigmine (0.04 mg/kg) over a period of 8 to 10 minutes during the anesthetic weaning process prior to moving a horse to the recovery stall.

Recovery quality, colic assessment, and gastrointestinal motility were determined as described for phase 1.

Statistical analysis—The statistical analysis was performed with commercially available software. Continuous data were reported as mean ± SD. Data with normal distributions as determined with Kolmogorov-Smirnov tests were analyzed by use of Student paired t tests. Interobserver differences for VAS scores were examined by use of a Pearson correlation coefficient. Values for 1 observer were then transformed to the
scale of the second observer by use of Passing-Bablok regression; the mean was then calculated for the VAS score for observer 1 and transformed VAS score for observer 2. Treatment differences were compared with a repeated-measures ANOVA. Nonnormally distributed data (including number of times a horse lifted its head but was unable to maintain it so the head fell back down against the floor, number of attempts to achieve sternal recumbency, and number of attempts to stand) and nominal data (including severity of muscle fasciculations, excitement, ataxia, and injury during recovery) were analyzed with Wilcoxon signed rank tests. Differences were considered significant at values of $P < 0.05$. 

Results

Results were obtained for the 3 phases of the study. Descriptive characteristics, surgical position, and surgical procedures were recorded for horses during each phase of the study (Table 1).

Phase 1 (neostigmine vs saline solution)—Only 5 of 6 horses enrolled in phase 1 completed the experiment. One horse died of colic (necropsy revealed a ruptured stomach secondary to a strangulating lipoma in the mesentery of the small intestines) 6 weeks after the first anesthetic episode, during which it had received an infusion of neostigmine. Data for this horse were censored in subsequent analyses.

Anesthetic events and objective recovery variables did not differ significantly between neostigmine or saline solution treatments (Table 2). Mean VAS scores for perfusion of the distal aspect of both forelimbs.

Table 1—Characteristics of 6 horses undergoing orthopedic procedures that were anesthetized with isoflurane and received neostigmine or saline (0.9% NaCl) solution prior to anesthetic recovery (phase 1), 7 horses used in a physostigmine dose-determining experiment (phase 2A), and 14 horses undergoing orthopedic procedures that were anesthetized with isoflurane and received neostigmine or physostigmine prior to recovery (phase 2B).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phase 1</th>
<th>Phase 2A</th>
<th>Phase 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breed</td>
<td>2 Morgans, 2 Holsteiners, 1 Standardbred, and 1 Paint</td>
<td>6 Quarter Horses and 1 Thoroughbred</td>
<td>12 Quarter Horses, 1 Thoroughbred, and 1 Hanoverian</td>
</tr>
<tr>
<td>Body weight (kg)*</td>
<td>582 ± 25.9</td>
<td>591 ± 72.9</td>
<td>525 ± 71.1</td>
</tr>
<tr>
<td>Sex</td>
<td>6 geldings</td>
<td>4 females</td>
<td>6 geldings and 8 females</td>
</tr>
<tr>
<td>Age (y)*</td>
<td>13.7 ± 2.4</td>
<td>6.0 ± 1.4</td>
<td>3.6 ± 1.7</td>
</tr>
<tr>
<td>Position during surgery</td>
<td>6 dorsal recumbency</td>
<td>NA</td>
<td>8 dorsal recumbency and 6 lateral recumbency</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>6 mandibular surgeries</td>
<td>NA</td>
<td>8 mandibular surgeries and 6 surgeries for perfusion of the distal aspect of both forelimbs</td>
</tr>
</tbody>
</table>

A blinded randomized, prospective crossover design was used for phases 1 and 2B.

*Value reported is mean ± SD.

NA = Not applicable.

Table 2—Anesthesia and recovery variables and overall quality of recovery from anesthesia for horses anesthetized with isoflurane and receiving injections of neostigmine or saline solution in phase 1 or physostigmine or neostigmine in phase 2B.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phase 1</th>
<th>Phase 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery quality score (mm)†</td>
<td>61 ± 12.0</td>
<td>71 ± 13.3^a</td>
</tr>
<tr>
<td>End-tidal isoflurane at end of anesthesia (%)</td>
<td>1.8 ± 0.0</td>
<td>1.6 (1.6–1.7)</td>
</tr>
<tr>
<td>Total duration of anesthesia (min)</td>
<td>173 ± 10.4</td>
<td>196 ± 12.3^a</td>
</tr>
<tr>
<td>Total duration of recovery (min)</td>
<td>24 ± 12.6</td>
<td>24 ± 8.5</td>
</tr>
<tr>
<td>Interval until first swallow (min)</td>
<td>4 ± 1.4</td>
<td>6 ± 2.0</td>
</tr>
<tr>
<td>Interval to first movement (min)</td>
<td>7 ± 3.5</td>
<td>10 ± 5.3</td>
</tr>
<tr>
<td>Interval to first attempt at sternal recumbency (min)</td>
<td>6 (3–12)</td>
<td>8 (5–25)</td>
</tr>
<tr>
<td>Interval to first time a horse lifted its head but it fell back down to the floor</td>
<td>1 (0–4)</td>
<td>1 (0–5)</td>
</tr>
<tr>
<td>No. of attempts to achieve sternal recumbency</td>
<td>4 (2–5)</td>
<td>2 ± 1.3^a</td>
</tr>
<tr>
<td>No. of attempts to achieve standing</td>
<td>6 (3–9)</td>
<td>2 ± 1.1^*</td>
</tr>
</tbody>
</table>

Values reported are mean ± SD and median (range). Events for assessment of recovery quality were measured from the time of discontinuation of anesthesia.

*Only 5 horses received saline solution because 1 horse died of colic after the first anesthetic episode. †Recovery quality was scored on a VAS scale of 100 mm indicating the best recovery possible (observers placed a mark on a 100-mm line segment corresponding to their interpretation of the patient’s recovery quality; scores were assigned by measuring the distance from the left end point to the point marked by the investigator, with 0 mm indicating the worst recovery possible and 100 mm indicating the best recovery possible).

During phase 2B, values in a row with different superscript letters differ significantly ($P < 0.05$).
Gastrointestinal motility was determined at the time a horse was able to stand and 1, 2, and 3 hours after standing (Figure 1). Number and intensity of gastrointestinal sounds at the time a horse was able to stand were significantly increased for horses after infusion of neostigmine, compared with results for horses after infusion of saline solution, because most horses had a decrease in gastrointestinal motility after infusion of saline solution. Gastrointestinal sounds were significantly increased for horses after infusion of neostigmine at the time a horse was able to stand, compared with results at 1, 2, and 3 hours after standing.

Phase 2A (physostigmine dose-determining experiment)—The physostigmine dose required to induce an increase in the number and intensity of borborygmi but that did not induce immediate signs of colic or excitement in 4 horses was 0.04 mg/kg. IV. One horse urinated and defecated after receiving the total dose (0.04 mg/kg) of physostigmine, and another horse developed signs of colic (pawing the ground, restlessness, rolling, and tachycardia) 1 hour after physostigmine administration; those signs of colic lasted for approximately 10 minutes and resolved without treatment. For the 3 additional horses, 2 occasionally pawed the ground during the first 30 minutes after injection. All other horses did not have signs of colic or excitement at all other time points.

Phase 2B (physostigmine vs neostigmine)—All 14 horses enrolled in phase 2B completed the experiment. Anesthetic events and objective recovery variables were determined (Table 2). Mean ± SD total anesthesia time was significantly longer after infusion of physostigmine (196 ± 12.3 minutes) than after infusion of neostigmine (184 ± 11.4 minutes). Physostigmine infusion resulted in significantly fewer attempts to achieve sternal recumbency (2 ± 1.3) and attempts until a horse was able to stand (2 ± 1.1), compared with results after neostigmine infusion (3 ± 1.2 and 3 ± 1.6, respectively). Horses had a significantly higher mean ± SD VAS score after physostigmine infusion (71 ± 13.3 mm) than after neostigmine infusion (62 ± 12.8 mm). There was good interobserver agreement ($R^2 = 0.7$) between the observers, who separately scored recovery quality. Severity of muscle fasciculations, excitement, ataxia, and injury judged as none, mild, moderate, or severe from the mean values for the 2 observers did not differ significantly between treatments. Significantly more horses defecated during recovery after infusion of neostigmine (4/5) than after infusion of saline solution (0/5). One horse urinated during recovery after infusion of neostigmine, but none of the horses urinated during recovery after infusion of saline solution. Fecal consistency was soft or liquid in horses that defecated during recovery. Signs of colic were detected during recovery from anesthesia in 3 of 6 horses after infusion of neostigmine and 4 of 5 horses after infusion of saline solution.

The incidence of colic during the 3 hours after recovery from anesthesia did not differ significantly between treatments. Gastrointestinal motility was determined at the time a horse was able to stand and 1, 2, and 3 hours after standing (Figure 1). Number and intensity of gastrointestinal sounds at the time a horse was able to stand were significantly increased for horses after infusion of neostigmine, compared with results for horses after infusion of saline solution, because most horses had a decrease in gastrointestinal motility after infusion of saline solution. Gastrointestinal sounds were significantly increased for horses after infusion of neostigmine at the time a horse was able to stand, compared with results at 1, 2, and 3 hours after standing.

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The incidence of colic did not differ between physostigmine (2/14) and neostigmine (6/14) treatments. Gastrointestinal motility was evaluated at the time a horse was able to stand after recovery from anesthesia and 1, 2, and 3 hours after standing (Figure 1). Administration of neostigmine and physostigmine significantly decreased gastrointestinal motility at 1, 2, and 3 hours after standing, compared with gastrointestinal motility at the time a horse was able to stand. One horse had a total lack of gastrointestinal sounds in all 4 quadrants at 2 hours after standing following infusion with physostigmine and developed signs of severe abdominal pain that required administration of analgesics prior to hour 3 after standing. Colic and gastrointestinal scoring were not performed on this horse for the 3-hour time point. Treatment with analgesics and IV administration of fluids successfully resolved the signs of abdominal discomfort.

Discussion

Analysis of results of the study reported here revealed a beneficial effect of central inhibition of acetylcholinesterase activity, compared with peripheral acetylcholinesterase inhibition or effects of saline solution, in horses recovering from anesthesia with isoflurane. Horses receiving physostigmine, a peripherally and centrally acting acetylcholinesterase inhibitor, but not neostigmine, an acetylcholinesterase inhibitor generally not able to penetrate the CNS, had fewer attempts to achieve sternal recumbency, fewer attempts to achieve standing, and a better quality of recovery as judged by an increase in the VAS score of approximately 10%. Because of a small sample size and increased variation attributable to surgical stimuli, significant differences in VAS responses attributable to physostigmine suggests the possibility that there may also be a large and clinically important treatment effect. Physostigmine and neostigmine did not pose a greater risk for the development of postoperative colic, compared with results for saline solution.

Acetylcholinesterase inhibitors block the enzymatic breakdown of acetylcholine in the cholinergic synapses, thereby increasing the availability of acetylcholine to bind nicotinic and muscarinic receptors. Activation of muscarinic and nicotinic receptors plays an integral role in the CNS in modulating neuronal signaling involved in cognitive behavior, consciousness, and memory. Cholinergic deficiency as a result of central inhibition during anesthesia predisposes patients to agitation, disorientation, or delirium during anesthetic recovery. Peripheral afferent input to the CNS as a result of activation of neuromuscular junctions may also contribute to the level of arousal. Sudden system-wide release of acetylcholine following administration of an acetylcholinesterase inhibitor with peripheral (neostigmine) or central (physostigmine) effects may increase simultaneous activation of neuromuscular junctions, thereby enhancing central responses to a bombardment of afferent signals that contribute to facilitating recovery from anesthesia.

Numerous drugs administered in the perioperative period can antagonize or inhibit the M1. Ketamine increases the activity of acetylcholinesterase in the cortex and hippocampus, which is a mechanism thought to contribute to cognitive disturbances associated with its use. It is speculated that isoflurane-, sevoflurane-, and halothane-induced suppression of acetylcholine release in the cerebral cortex and midbrain contributes to the anesthetic effects of these drugs, although specific acetylcholine antagonists have not been found to be clinically useful as anesthetics. In addition, inhalation anesthetics can inhibit both muscarinic and nicotinic acetylcholine receptors at concentrations at or below the minimum alveolar concentration. Opioids such as morphine and fentanyl at clinically relevant doses block presynaptic release of acetylcholine, which reduces the availability for binding the M1. Barbiturates and propofol also act as M1 antagonists in a dose-dependent manner. Additionally, the parasympatholytic agents atropine and scopolamine cross the blood-brain barrier to block the central postsynaptic M1. Many of the drugs are, or historically have been, routinely used in anesthesia of horses and thus could contribute to emergence delirium. Horses recovering from inhalation anesthesia may be disoriented and uncoordinated or may display delirious behavior that predisposes them to injury (potentially fatal) when attempting to stand. Results for the present study provided evidence that central cholinergic inhibition may contribute to poor recovery quality in horses.

Recovery quality is impacted by many factors, including breed of horse; temperament and past events that may have an effect on the patient; preexisting stress or disease; duration of anesthesia; use of drugs that contribute to excessive sedation, ataxia, or muscle weakness; hypotension during anesthesia; poor positioning or inadequate use of padding during anesthesia; pain; and duration of recovery. In the present study, the anesthetic drug protocol was identical in all experiments and each horse served as its own control animal for treatment comparisons to minimize breed and temperament effects. Preanesthetic sedation was adequate in all horses because no horses had signs of excitement before anesthetic induction. Preemptive analgesia was provided by IV administration of morphine and oral administration of phenylbutazone (1 mg/kg) to all horses before anesthetic induction. Additional sedatives or analgesics were not administered before recovery to ensure that we did not obscure acetylcholinesterase inhibitor effects. Pain was assessed when a horse was able to stand and hourly for 3 hours after standing. One horse receiving saline solution, 1 horse receiving neostigmine, and 1 horses receiving physostigmine required treatment for signs of pain related to the surgical procedure between 2 and 3 hours after standing; thus, differences in pain did not appear to be a major confounding factor in recovery quality immediately after anesthesia in the present study. Mean arterial blood pressure was maintained at > 70 mm Hg throughout the anesthetic period, and appropriate positioning and padding were provided for all anesthetic episodes to prevent myopathy. The target duration for each anesthetic episode was 180 minutes; however, this amount of time sometimes was not exceeded because of surgical demands. In phase 2B, horses had a significantly longer duration of anesthesia when receiving physostigmine.
Physostigmine than when receiving neostigmine. Increased duration of anesthesia results in increased saturation of tissues with volatile anesthetic and leads to prolongation of the recovery period. In 1 study, anesthesia duration > 165 minutes was correlated with reduced recovery quality from anesthesia in horses recovering after surgery for colic. Despite the significantly greater duration of anesthesia when horses received physostigmine, these horses still had equivalent recovery times and superior recovery qualities to those for horses receiving neostigmine. Therefore, it appears possible that the longer duration of anesthesia when horses received physostigmine may have resulted in underestimation of the recovery benefit for that treatment.

Inhalation anesthetics can cause concentration-dependent impairment of motor coordination, muscle strength, and alertness in horses. Accordingly, minimizing the concentration of inhalation anesthetic during the recovery period should improve coordination, strength, and alertness. Prolonging the recovery period typically improves the quality of recovery after inhalation anesthesia. Analysis of results of the present study suggested that a concentration-dependent decrease in inhibition of central acetylcholine receptors corresponding to time-dependent washout of the inhaled anesthetic may be a possible mechanism for this effect.

Although none of the treatments resulted in an increased incidence of colic, visual inspection of the data suggested a pattern for a decrease in the frequency of signs of colic when horses received physostigmine, compared with results when horses received neostigmine or saline solution. Lack of significant differences among treatments could have been the result of insufficient statistical power (type II error). One horse had colic after infusion of physostigmine that was treated successfully with analgesics. The horse had a lack of gastrointestinal sounds at the time when the signs of colic were most severe. Colic in horses is often associated with reduced gastrointestinal motility, and neostigmine has been administered to increase motility in horses with large colon impactions; however, increased gastrointestinal motility has also been associated with abdominal pain.

Postanesthetic administration of physostigmine may improve gastrointestinal tract motility and function, rather than increasing the risk of colic. Anesthetics and the effects of prolonged withholding of food on gastrointestinal transit time are typically associated with reduced intestinal motility and an increased risk of impaction colic, compared with results for nonanesthetized horses. Administration of an acetylcholinesterase inhibitor in the present study increased the number and intensity of borborygmi in the immediate postoperative period, compared with results prior to anesthesia, as evidenced by fewer quadrants with a decrease in or absence of gastrointestinal sounds. Acetylcholine is one of the major neurotransmitters of the enteric nervous system responsible for controlling and coordinating gastrointestinal motility with a general effect of causing gastric smooth muscle contraction.

Horses receiving physostigmine had the lowest incidence of colic and also had a high incidence of increased gastrointestinal motility at the time a horse was able to stand, whereas horses receiving saline solution had the highest incidence of colic but had no abdominal quadrants with increased gastrointestinal sounds. Thus, administration of physostigmine for the prevention of emergence delirium from inhalation anesthesia also may promote intestinal motility after recovery.

Analysis of results of the present study suggested that reversing central cholinergic blockade led to improved anesthetic recovery quality in horses during recovery from anesthesia with isoflurane. Uninhibited central cholinergic transmission leading to improved alertness and cognitive function during recovery from anesthesia with isoflurane may be responsible for the perceived benefit for recovery quality; however, further studies are required to confirm this mechanism. The potential benefits of physostigmine, compared with potential benefits for conventional postanesthetic sedatives such as β2-adrenoreceptor agonists or phenothiazines, have not been investigated. Similarly, pharmacological interactions between physostigmine and conventional sedatives in horses recovering from anesthesia have not been evaluated. However, physostigmine may offer a means to improve anesthetic recovery quality in equine patients and thus decrease the exceptionally high perioperative morbidity and fatality rates in this species.

References


