Colic and lameness represent 2 of the biggest causes of morbidity and fatalities in horses throughout the world.1–3 The most commonly used analgesics in horses are the nonsteroidal anti-inflammatory drugs flunixin meglumine and phenylbutazone, both of which can be associated with effects on the gastrointestinal tract, such as gastric ulcers and right dorsal colitis.4–6 In other species, opioids, including fentanyl, buprenorphine, and morphine, are commonly used as analgesics for animals with moderate to severe pain.7–9

Effect of acepromazine, butorphanol, or N-butylscopolammonium bromide on visceral and somatic nociception and duodenal motility in conscious horses

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Objective—To evaluate effects of butorphanol, acepromazine, and N-butylscopolammonium bromide (NBB) on visceral and somatic nociception and duodenal motility in conscious, healthy horses.

Animals—6 adult horses.

Procedures—Visceral nociception was evaluated by use of colorectal distention (CRD) and duodenal distention (DD) threshold. Somatic nociception was evaluated via thermal threshold (TT). Nose-to-ground height, heart rate, and respiratory rate were also measured. Each horse received each treatment in randomized order; investigators were not aware of treatments. Butorphanol was administered IV as a bolus (18 µg/kg) followed by constant rate infusion at 13 µg/kg/h for 2 hours, whereas acepromazine (0.04 mg/kg), NBB (0.3 mg/kg), and saline (0.9% NaCl) solution (2 mL) were administered IV as a bolus followed by constant rate infusion with saline solution (10 mL/h) for 2 hours. Variables were measured before and for 3 hours after treatment. Data were analyzed by use of a 3-factor ANOVA followed by a Bonferroni t test for multiple comparisons.

Results—Nose-to-ground height decreased after acepromazine. Respiratory rate decreased after acepromazine and increased after butorphanol. Heart rate increased briefly after NBB. Some horses had an increase in TT after butorphanol and acepromazine, but there was not a significant treatment effect over time. Drug effect on DD or motility was not evident. The CRD threshold increased significantly at 5, 65, 155, and 185 minutes after acepromazine and from 5 to 65 minutes after NBB.

Conclusions and Clinical Relevance—Each drug caused predictable changes in sedation and vital signs, but consistent antinociceptive effects were not evident. (Am J Vet Res 2008;69:579–585)
Phenothiazine tranquilizers decrease smooth muscle tone and peristalsis, probably through a depression effect on peripheral anticholinergic action; however, despite the widespread use of acepromazine, little is known about its effects on the gastrointestinal tract. Use of a liquid marker revealed that acepromazine delays gastric emptying in ponies. Acepromazine can alter activity of esophageal smooth muscle, which induces a relaxant effect and a change in the peristaltic pattern. In a study in which investigators used 3 ponies prepared with Thrill-Vella loops (ie, isolated segments of jejunum), bipolar electrodes, and strain gauge transducers, acepromazine reduced electrical activity, compared with baseline values, but volume transport through the gastrointestinal tract was increased. In a study to evaluate experimentally induced visceral pain in cats (inflation of a rectal balloon), the addition of acepromazine to butorphanol and oxymorphone significantly increased the degree of antinociception.

Hemodynamic advantages of acepromazine may be lost in volume-depleted animals; however, many horses with signs of abdominal pain attributable to so-called spasmodic colic are not dehydrated, and assuming intestinal effects of acepromazine are beneficial, it could be a useful drug in the management of these affected horses. The α₂-adrenergic receptor agonists are commonly used in horses with signs of abdominal pain to provide analgesia and sedation, yet these agonists have important negative effects on cardiopulmonary function.

The synthetic opioid butorphanol is an agonist at κ (ie, OP2) receptors but an antagonist at μ (ie, OP3) receptors. When administered by bolus injection, butorphanol provides a moderate degree of somatic analgesia and a slightly greater degree of visceral analgesia in horses; however, it also causes decreases in gastrointestinal tract motility. It has been suggested that administration of this agent via CRI reduces the adverse effects on gastrointestinal tract motility, but objective data about the analgesic efficacy for this protocol are limited. In a study, investigators reported that the clinical efficacy of butorphanol administered via CRI in postoperative colic patients had definite promise for analgesia without substantial risk of postoperative ileus. Thus, objective analysis of this protocol for somatic and visceral analgesia as well as gastrointestinal tract motility would provide much needed direct evidence for expanding the clinical use of CRI of butorphanol in horses with lameness as well as in nonstrangulating or postoperative colic patients.

N-butylscopolammonium bromide has anticholinergic and antispasmodic properties and has been commercially available in Europe (in combination with hyoscine) for the treatment of horses with spasmodic colic for many years. It has recently been approved (without hyoscine) for similar use in the United States. In experiments in which distention of a cecal balloon was used, NBB had an analgesic effect in 6 of 8 ponies in 1 study. In a similar study, NBB had a brief analgesic effect as well as a transient negative effect on cecal contractions in ponies. Thus, the objective of the study reported here was to use each of 3 drugs (butorphanol, acepromazine, and NBB) at commonly used clinical dosages to evaluate visceral and somatic nociception and duodenal motility in conscious, clinically normal horses. Our hypotheses were that each drug would provide significant visceral antinociception in conscious horses, that only butorphanol would provide significant somatic antinociception, and that NBB and butorphanol (but not acepromazine) would decrease duodenal motility.

Materials and Methods

Animals—Six adult Thoroughbred or Thoroughbred-crossbred horses (3 mares and 3 geldings; mean age, 13.2 years [range, 7 to 23 years]; mean body weight, 538 kg [range, 485 to 608 kg]) were used in the study. Each had a permanently implanted gastric cannula, which had been inserted at least 2 years prior to the start of the study. Between trials, horses were housed on pasture, where they had unlimited access to water, a mineral block, paddock grass, and coastal hay and received sweet feed twice daily to maintain body condition. All horses were clinically normal with no evidence of gastrointestinal tract disease. Horses were moved to a stall 12 to 18 hours prior to each trial, where they had unlimited access to water but not to feed. Mares were used during behavioral diestrus. All procedures were approved by the University of Florida Institutional Animal Care and Use Committee (protocol No. E164).

Treatments—For the experimental procedures, each horse was restrained in stocks by lead ropes loosely attached to the halter; all horses were familiar with the testing procedures. A minimum of 1 week was allowed between treatments. Each horse received each of 4 treatments (physiologic saline [0.9% NaCl] solution, butorphanol tartrate, acepromazine maleate, and NBB) in accordance with a randomized block design. Saline solution was administered IV as a bolus injection of 2 mL followed by CRI of saline solution at 10 mL/h for 2 hours. Butorphanol was administered IV as a bolus (18 μg/kg) followed by CRI (13 μg/kg/h diluted in saline solution to achieve a final rate of 10 mL/h) for 2 hours. Acepromazine was administered IV as a bolus (0.04 mg/kg) followed by CRI of saline solution at 10 mL/h for 2 hours. The NBB was administered IV as a bolus (0.3 mg/kg) followed by CRI of saline solution at 10 mL/h for 2 hours. Bolus doses were administered in ≤5 seconds. All CRIs were accomplished by use of a syringe pump.

Thermal threshold—Thermal threshold was determined as described elsewhere. Briefly, a probe with heater and temperature sensor elements was placed flat on a shaved area over the most-dorsal aspect of the shoulders (ie, withers) of each horse and connected to a threshold testing device by use of a long cable that enabled the horses to move during and between tests. A cutoff point of 45°C was used to prevent thermal burns. Probes were calibrated prior to attachment to each horse and allowed to equilibrate to skin temperature for at least 10 minutes prior to testing. A positive response was recorded when a horse twitched its withers or turned its head to look at its side.
Colorectal distention—Colorectal distention was performed as described elsewhere. Briefly, a 45-cm diameter balloon (total capacity of 12 L) attached to pressure and transducer tubing was placed within the rectum at a point 45 to 30 cm proximal to the external anal sphincter. Balloon distention was computer controlled by use of an electronic barostat, and a ramp distention protocol (2 mm Hg at the start, which was followed by increases of 2 mm Hg every 20 seconds) was initiated. Maximum pressure was 45 mm Hg. Expulsion of the balloon was considered a positive response.

Duodenal distention and motility—The gastric cannula was opened. Residual stomach contents were flushed from the cannula, and the cannula was drained. Balloon placement and the duodenal distention protocol were similar to those described elsewhere. Briefly, endoscopic guidance was used to insert a 20-cm diameter balloon approximately 100 cm aborad to the gastroduodenal sphincter. Inflation was controlled by use of an electronic barostat (15 mm Hg at the start, which was followed by increases of 5 mm Hg every 60 seconds). Maximum pressure was 45 mm Hg. A positive response required at least 2 signs of abdominal discomfort (pawing the ground, looking at the flank, rapid shifting of weight bearing in the hind limbs, kicking at the abdomen, or a flehmen reaction).

Between distention periods, the balloon was maintained at a baseline pressure of 2 mm Hg. Continuous volume or pressure recordings were used for the assessment of duodenal motility. Two variables were used to assess motility. A contraction was defined as a deflection of pressure > 5 mm Hg from the baseline pressure. Frequency was defined as the number of contractions per unit time. Amplitude of a given contraction was defined as the deflection of pressure from the baseline pressure. Frequency and amplitude were each compiled in 15-minute blocks for the duration of each experiment, and periods during duodenal distentions were excluded.

Measurement of variables—Investigators who recorded all data were unaware of the treatment administered to each horse. Prior to each treatment, thermal threshold was measured 3 times with at least a 15-minute interval between measurements. Colorectal distention, heart rate (by manual palpation of the facial artery), respiratory rate (by visual observation), general attitude, and nose-to-ground distance were measured once prior to initiation of treatment, whereas duodenal distention was measured twice prior to initiation of treatment. Tape measures permanently attached to the stocks were used for determination of the nose-to-ground distance.

Initial injection of the treatments was designated as time 0. All measurements were conducted again 5 minutes after initial administration. Thereafter, attitude, thermal threshold, heart rate, respiratory rate, and nose-to-ground distance were determined every 15 minutes for 3 hours, whereas colorectal distention and duodenal distention thresholds were determined every 30 minutes for 3 hours. Testing order for colorectal distention and duodenal distention was randomly assigned by a coin toss. When thermal, duodenal, and colorectal threshold measurements were conducted at the same time point, thermal threshold was always determined first.

Statistical analysis—When a horse reached the maximum allowable value for a given response variable, the maximum value was used as the threshold response for that variable. Data were analyzed by use of a split-plot ANOVA in accordance with the model Y = treatment + period + horse + error, + time + (treatment X time) + error,. where Y is the response variable, error, is error for treatment and period, and error, is error for time and treatment X time. Response variables were skin temperature, thermal threshold, colorectal distention pressure, duodenal distention pressure, nose-to-ground distance, heart rate, and respiratory rate. Because period was not a significant factor for any of the response variables, period was eliminated from each model and data were then analyzed by use of a 3-factor ANOVA with the fixed factors of time and treatment and the random factor of horse. When significant main effects or interactions were detected, post hoc comparisons were made by use of the Bonferroni t test. A commercial software program was used for all analyses, and values of P < 0.05 were considered significant. For post hoc comparisons, the critical value of P = 0.05 was divided by the number of comparisons.

Results

Animals—Overall, all treatments were tolerated well by most horses. One horse became agitated and had evidence of visceral discomfort consistent with clinical signs of colic immediately after NBB administration. This behavior resolved after treatment with xylazine hydrochloride and flunixin meglumine, but experimental evaluation was discontinued immediately and NBB was not readministered to that horse. No other adverse events or alterations in general attitude were detected.

Heart rate—After NBB administration, heart rate was increased from 5 to 35 minutes, compared with the value at time 0 (Figure 1). Heart rate was also increased after NBB administration, compared with the rate after butorphanol administration from 5 to 30 minutes and after administration of saline solution and acepromazine from 5 to 80 minutes.

Respiratory rate—After butorphanol administration, respiratory rate was increased from 125 to 185 minutes, compared with the rate at time 0 (Figure 2). Butorphanol administration also resulted in a significant increase in respiratory rate, compared with the rate after administration of acepromazine, from 50 to 185 minutes. Acepromazine administration resulted in a decreased respiratory rate, compared with the rate after administration of saline solution at 110, 155, 170, and 185 minutes and after administration of NBB from 95 to 125 minutes and again at 170 minutes.

Nose-to-ground height—After acepromazine administration, the nose-to-ground height was significantly less, compared with the height at time 0. (Figure 3). Nose-to-ground height after administration of acepromazine was also significantly less, compared
with height after administration of butorphanol and NBB at 20 to 185 minutes and after administration of saline solution from 20 to 170 minutes.

**Thermal threshold**—One horse did not respond to the thermal threshold device; thus, data were available for only 5 horses. Twenty minutes after butorphanol administration, mean ± SD thermal threshold (44.7 ± 0.6°C) was significantly higher, compared with the value at time 0 (41.2 ± 1.1°C). Thermal threshold at 20 minutes after butorphanol administration also was significantly higher, compared with values at the same time point after administration of saline solution (40.2 ± 2.3°C), acepromazine (40.9 ± 2.0°C), and NBB (41.1 ± 2.4°C). A few other sporadic significant differences were detected, including a higher thermal threshold at 50 minutes after acepromazine administration, compared with the value after administration of saline solution (43.9 ± 2.7°C and 40.7 ± 2.0°C, respectively), and a higher threshold at 125 minutes after administration of acepromazine, compared with the value after administration of NBB (43.9 ± 1.9°C and 40.4 ± 1.6°C, respectively). Thermal threshold was significantly lower 185 minutes after administration of saline solution, compared with the value at time 0 (38.9 ± 1.1°C and 42.9 ± 0.7°C, respectively). At 185 minutes after administration of saline solution, thermal threshold was also significantly lower, compared with values after administration of acepromazine (43.2 ± 1.5°C) and NBB (43.1 ± 1.4°C).

**Colorectal distention threshold**—The colorectal distention threshold was increased at 5, 65, 155, and 185 minutes after acepromazine administration, compared with the value at time 0 (Figure 4). Acepromazine also caused an increase in colorectal distention threshold, compared with values after administration of saline solution and butorphanol at 65, 125, 155, and 185 minutes and after administration of NBB at 155 and 185 minutes after administration of saline solution, compared with the value at time 0 (38.9 ± 1.1°C and 42.9 ± 0.7°C, respectively). At 185 minutes after administration of saline solution, thermal threshold was also significantly lower, compared with values after administration of acepromazine (43.2 ± 1.5°C) and NBB (43.1 ± 1.4°C).
185 minutes. The threshold was increased at 5, 35, and 65 minutes after NBB administration, compared with the value at time 0. The colorectal threshold was also increased after administration of NBB, compared with the value after administration of saline solution at 5 minutes and after administration of butorphanol at 35 minutes.

**Duodenal distention threshold**—Because of the anatomic location of the gastric cannula, insertion of the duodenal balloon was not possible in 1 horse. Therefore, data on duodenal distention and motility were available for only 5 horses. There were no significant differences among treatments. There was an overall decrease in duodenal distention threshold from 65 to 185 minutes, compared with the value at baseline (Figure 5).

**Duodenal motility**—We did not detect significant differences among treatments for frequency or amplitude of duodenal contractions. For all treatments, amplitude was decreased from 15 to 195 minutes and frequency was decreased from 105 to 195 minutes, compared with the amplitude and frequency, respectively, at time 0. When evaluating individual motility tracings, an immediate profound effect of NBB administration was apparent, but this effect was extremely brief (15 to 20 minutes; Figure 6).

**Discussion**

Butorphanol administration provided a brief period of somatic antinociception but a nonsignificant alteration in indices of visceral antinociception. Because the SD was greater than expected in some measurements, the sample size used in the study reported here may have precluded detection of a small difference between treatments (type II error). This may be especially true for the thermal threshold measurements after butorphanol administration because many horses received the maximum temperature; thus, they were recorded as 43°C even though their actual threshold may have been higher. In addition, large individual variations in thermal antinociception have been reported for butorphanol in other species, with some animals being considered nonresponders.\(^{35,36}\)

Regardless of the constraints attributable to sample size, all visceral threshold measurements decreased after bolus administration and any pattern toward an effect was not continued throughout the CRI of butorphanol. This differs from a clinical report\(^{29}\) whereby there was a reduction in pain scores after colic surgery during a 24-hour infusion of butorphanol. This could have been because butorphanol administration decreased the initial painful stimuli immediately after surgery, which thus prevented a wind-up phenomenon. Butorphanol administered IV as a bolus has provided somatic and visceral antinociception in other horses with experimentally induced pain,\(^{37–39}\) and in cats it provided somatic antinociception.\(^{35}\)

Administration of NBB resulted in tachycardia and visceral antinociception, which was indicated by a significant increase in colorectal distention threshold and a slight but nonsignificant increase in duodenal distention threshold. These changes were of short duration (15 to 20 minutes), which is similar to results in other reports.\(^{30,31}\) The effect of NBB on duodenal motility was obvious and consistent when evaluation of the individ-
ual traces for each horse was conducted. But because the group × time interaction was not significant (P = 0.228), any subsequent comparisons could not be made with statistical confidence. Thus, this could have been a type II error and would need a larger sample size or, potentially, to be broken down into smaller time periods immediately following the bolus injection to make this conclusion. Administration of a combination of NBB and hyoscine can decreaseecal contractions for 20 minutes. In that study, the NBB-hyoscine combination did not provide an antinociceptive effect. Butorphanol and NBB have similar periods of visceral anti-nociception after bolus injection at dosages of 0.1 and 0.3 mg/kg, respectively, in horses with experimentally induced colonic distension.

Acetomazine administration resulted in prolonged sedation, which was indicated by a decrease in nose-to-ground height. Acetomazine administration also resulted in a decrease in respiratory rate, as well as an increase in colorectal distention threshold, at various time points later in the study. A reason for these effects was not clear because these changes did not coincide with the peak period of sedation (35 minutes) or with each other. Although typically classified as a sedative without analgesic effects, acetomazine has minimum alveolar concentration–sparing effects for halothane when administered alone or in conjunction with butorphanol, whereas butorphanol has an inconsistent effect.

The difference between alterations in duodenal and colorectal distention thresholds was likely related to the criteria used for a positive response. Because expulsion of the balloon was used for determination of the colorectal distention threshold, this may have been related to an urge-to-defecate endpoint, rather than an endpoint for a noxious stimulus. This is consistent with the lower threshold pressures detected with this testing modality. In other species, pressures > 40 to 60 mm Hg are considered noxious. Thus, the acetomazine-related alteration in colorectal distention threshold may have been related to sedation and alteration of the urge-to-defecate response, rather than to true visceral analgesia.

Each treatment in the study reported here caused a predictable change in sedation or vital signs. Butorphanol administration resulted in a brief somatic antinociceptive effect, and butorphanol, acetomazine, or NBB administration resulted in a visceral colorectal distention antinociceptive effect of varying duration. Also, none of the treatments caused a significant decrease in duodenal motility, although administration of NBB consistently resulted in a visual change in motility pattern of extremely short duration. From a clinical perspective, the negative effects of butorphanol administration on duodenal motility may be limited to bolus injection. However, additional investigations into the effects of prolonged administration of butorphanol via CRI are warranted.

References:


