Cardiopulmonary effects of buprenorphine in horses

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Objective—To investigate the effects of buprenorphine on cardiopulmonary variables and on abdominal auscultation scores in horses.

Animals—6 healthy adult horses.

Procedures—Horses were restrained in stocks and allocated to 2 treatments in a randomized crossover design, with 1-week intervals between each treatment. Saline (0.9% NaCl) solution was administered IV as a control, whereas buprenorphine (10 μg/kg, IV) was administered to the experimental group. Cardiopulmonary data were collected for 120 minutes after buprenorphine or saline solution administration. Abdominal auscultation scores were monitored for 2 and 12 hours after drug administration in the control and experimental groups, respectively.

Results—Following control treatment, horses remained calm while restrained in the stocks and no significant changes in cardiopulmonary variables were observed throughout the study. Buprenorphine administration caused excitatory phenomena (restlessness and head shaking). Heart rate, cardiac index, and arterial blood pressure were significantly increased after buprenorphine administration until the end of the observational period (120 minutes). Minimal changes were found in arterial blood gas tensions. Abdominal auscultation scores decreased significantly from baseline for 4 hours after buprenorphine administration.

Conclusions and Clinical Relevance—Buprenorphine induced excitement and hemodynamic stimulation with minimal changes in arterial blood gas tensions. These effects may impact the clinical use of buprenorphine in horses. Further studies are indicated to investigate the effects of buprenorphine on gastrointestinal motility and fecal output. (Am J Vet Res 2006;67:1675–1680)

Opioid agents are widely used in veterinary medicine because of their analgesic effects. These drugs produce their effects by interacting with opioid receptors located in the CNS and in peripheral tissues, namely μ, κ, and δ receptors.1 Stimulation of μ opioid receptors is responsible for analgesia, excitatory phenomena, constipation, bradycardia, and respiratory depression, whereas a κ agonist causes some analgesic effect with less interference with gastrointestinal motility and less respiratory depression.1,4 Opioid agents have an important role in pain management in small animals. However, their use is still limited in horses because of the possibility of excitation and a clinically relevant decrease in gastrointestinal motility.1,5,6 Although opioid agonists may induce behavioral changes such as increased locomotor activity in healthy horses, pure κ opioid agonists, such as U50488H, appear to cause less interference with the normal gastrointestinal motility pattern, compared with μ agonists, such as fentanyl and morphine.1,5,6

Buprenorphine is a semisynthetic, highly lipophilic opioid agent that acts as a partial agonist at μ receptors.6 Buprenorphine has a bell-shaped dose response curve with respect to analgesia in rodents, with increasing doses resulting in less analgesia in this species.10 The effects of buprenorphine on the cardiopulmonary system are minimal in humans and dogs.11,12 Only a few reports13–15 exist on the use of buprenorphine in the equine species. Buprenorphine has been evaluated in combination with α2-agonist receptor agonists and with acepromazine to produce chemical restraint in horses.15 To our knowledge, results of the only published study6 evaluating the isolated use of buprenorphine (3 μg/kg, IV) in healthy horses and in horses with chronic obstructive pulmonary disease revealed that this drug induced an excitatory phenomenon with an increased HR and arterial blood pressure but did not induce clinically relevant changes in pulmonary function. In that study, however, the effects of buprenorphine on CO and gastrointestinal motility were not evaluated. In a prelimi...
nary study, IV administration of buprenorphine at 10 μg/kg resulted in an increase in the latency period of the skin twitch reflex in response to radiant light heat directed onto the withers during a 6 hour period in comparison to control horses, providing evidence for an analgesic effect of this opioid agent in horses.

The objective of the present study was to evaluate the cardiopulmonary effects of buprenorphine in horses. In addition, the effects of this opioid agent on abdominal auscultation scores were also assessed.

Materials and Methods

Animals—The present study was approved by the institutional animal care committee. Six healthy adult horses (3 male and 3 female) weighing 360 ± 24 kg (mean ± SD) were used. Health status was assessed by means of clinical examination, CBC determination, and blood gas tension analysis.

Instrumentation and data sample collection—Each horse was previously acclimatized to the experimentation room and conditioned to remain undisturbed for approximately 3 hours restrained in a stock to allow instrumentation and cardiopulmonary data collection during the experiment. On the day before the study, each horse was placed in individual stalls, with food and water provided ad libitum. Hay and commercial food was given in the morning at 7 AM. One hour later, each horse was restrained in a stock for instrumentation. During the period of instrumentation and data sample collection, movement of all personnel involved in the study and all conversations were reduced to the minimal necessary to avoid environmental stimulation of the horses involved in the study. To minimize restlessness associated with prolonged restraining in stocks, small amounts of carrots and pellets of commercial food were regularly offered to all horses receiving both treatments, except during periods of data sample collection.

Adhesive electrodes were placed according to a base-apex lead attachment to display the ECG. Values of HR were obtained from ECG tracing. A local anesthetic solution (0.5 to 1.0 mL of 2% lidocaine) was injected SC over the left jugular vein before catheters were placed. Two 8.5-F catheter introducers were inserted approximately 30 cm apart in the left jugular vein. A 160-cm-long, balloon-tipped, flow-directed thermistor (WPI) was advanced through the cranial introducer and positioned in the cranial vena cava. A 160-cm-long, balloon-tipped, flow-directed catheter (WPI) was inserted into the transverse facial artery to measure CO. A thermistor located at the tip of the pulmonary artery catheter (WPI) was used. Hemodynamic variables were registered on the screen of the monitor.

Statistical analysis—Analysis was performed with a commercial software program. For each group, cardiopulmonary variables were analyzed by use of a 1-way ANOVA for repeated measures, followed by a Dunnet test to compare all sample collection times with baseline data (−30 minutes). Comparison between groups was performed by a 2-way ANOVA, followed by a paired t test to which a Bonferroni correction for multiple pairwise comparisons was applied. A Wilcoxon matched pairs test was used to compare abdominal auscultation scores obtained throughout the study with the baseline data (30 minutes). Values of P < 0.05 were considered significant. All parametric data are reported as mean ± SEM, whereas nonparametric data are reported as median and interquartile range.
Results

When horses received saline solution (control treatment), they remained calm throughout the observational time. On the other hand, buprenorphine administration induced a restlessness-excitatory phenomenon, as suggested by the observation of continuous head nodding, head shaking and neighing, and pawing and shifting of ground support in all 4 limbs. None of the horses had violent behavior or became ataxic after buprenorphine administration. Clinical signs of excitation started approximately 10 to 15 minutes after buprenorphine administration and were evident while the horses were restrained in the stocks for cardiopulmonary data collection. At the end of cardiopulmonary data collection, horses were returned to the stalls (120 minutes after buprenorphine or saline solution administration). When buprenorphine-treated horses were returned to the stall, a gross increase in locomotor activity was noticed until approximately 3 to 4 hours after opioid administration.

Following control treatment, with the exception of a transient increase in CI at 30 minutes, cardiovascular variables did not change from baseline throughout the experiment (Figure 1, Table 1). Buprenorphine administration caused sustained increases from baseline in HR, CI, SAP, DAP, and MAP, while SV and SVR did not change after buprenorphine administration. Treatment comparison revealed that HR, SAP, and MAP were significantly higher following buprenorphine treatment from 30 minutes until the end of the observational period (120 minutes). A transient decrease from baseline was found in MPAP prior to buprenorphine administration. Although core body temperature did not change following control treatment, this variable increased from 37.9

![Figure 1](image-url)

**Figure 1**—Effects of IV administration of saline (0.9% NaCl) solution (control treatment; open circles) or buprenorphine at 10 μg/kg (solid triangles) on RR, MAP, HR, core body temperature (BT), SVR, and CI in 6 horses. Values reported as mean ± SEM. Saline solution or buprenorphine was administered at time 0. *p*Within each group, value differs significantly (*P* < 0.05) from baseline value (–30 minutes). †Between groups, value differs significantly (*P* < 0.05).

<table>
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<th>30</th>
<th>60</th>
<th>90</th>
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<td>SV (mL/beat)</td>
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<td>97.0 ± 0.3</td>
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<td>96.8 ± 0.3</td>
<td>97.2 ± 0.4</td>
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*Significant (*P* < 0.05) difference from baseline value (–30 minutes). †Significant (*P* < 0.05) difference between groups.
to the degree of the patient discomfort. A previous dose of an opioid appears to be inversely proportional with signs of pain, excitatory phenomena are less likely to occur, as the risk of an adverse response to a fixed administration. In the experimental group, auscultation changes were detected for 2 hours after saline solution (median [interquartile range]. Saline solution or buprenorphine was administered at time 0. *Significant (P < 0.05) difference from baseline value. See Figure 1 for remainder of key.

± 0.1°C at baseline to 38.3 ± 0.2°C at the end of the observational period (120 minutes) following buprenorphine treatment.

No changes in arterial blood gas tensions were observed in the control group. Although RR increased from baseline after buprenorphine administration, no differences in PaO₂, PaCO₂, and SaO₂ were found in the experimental group (Table 1). Significant differences were observed for arterial pH values following buprenorphine treatment, but this variable remained within physiologic limits (pH, 7.35 to 7.46).

### Discussion

Excitement is a common adverse effect associated with the use of opioid agents in horses. This effect may be related to central dopaminergic activation and is more likely to occur when pure μ opioid agonists, such as morphine and fentanyl, are used in pain-free horses. Otherwise, when opioids are used in horses with signs of pain, excitatory phenomena are less likely to occur, as the risk of an adverse response to a fixed dose of an opioid appears to be inversely proportional to the degree of the patient discomfort. A previous study reported excitatory phenomena when buprenorphine was used in conscious pain-free horses. On the other hand, when buprenorphine (6 μg/kg) was combined with either xylazine (0.7 mg/kg) or acepromazine (0.05 mg/kg) to produce standing chemical restraint, satisfactory sedative effects were reported. However, the use of buprenorphine combined with α₂-adrenergic receptor agonists, such as xylazine and detomidine, appears to result in more effective sedative effects than buprenorphine-acepromazine combinations. Although horses receiving physiologic saline solution (placebo) remained calm and were easily restrained in the stocks throughout our study, buprenorphine-treated horses were difficult to maintain restrained in the stocks as a result of an excitation phenomenon induced by the opioid. An increase in muscular activity associated with the CNS stimulating effect of the opioid may explain the increase in core body temperature observed after buprenorphine administration.

Cardiovascular stimulation secondary to excitatory phenomena has been documented when buprenorphine and other opioids are used in horses with no signs of pain. The hemodynamic stimulation observed after buprenorphine in our study was probably the result of CNS stimulation leading to increased sympathetic outflow.

Buprenorphine increased HR values by 17% to 40% above baseline. Similar results were observed by Szoke et al, who observed that a smaller dose of buprenorphine (3 μg/kg) produced a 30% increase in HR. The CI was also significantly higher after buprenorphine administration in our study. At the end of the observational period following buprenorphine treatment, CI was increased by approximately 57% above baseline (from 61 ± 3 mL/kg/min at baseline to 96 ± 11 mL/kg/min at 120 minutes). In conscious resting horses, increased HR as a result of parasympathetic blockade induced by atropine sulphate does not change CO. In this instance, decreased SV attributable to reduced diastolic filling time prevents CO from increasing despite increased HR.

In our study, increased HR was coupled with increases in CI, whereas SV values remained unchanged after buprenorphine administration. Increased sympathetic outflow caused by the CNS stimulant effect of buprenorphine may explain these results. During sympathetic stimulation, SV is maintained or increased because of increased myocardial inotropism and shortened duration of systole.

In our study, MAP increased approximately 38% above baseline at 60 minutes after buprenorphine administration (from 113 ± 5 mm Hg to 156 ± 3 mm Hg). When a smaller dose of buprenorphine (3 μg/kg) was administered to conscious horses, MAP was increased by 18% above baseline at a similar time period. The increase in arterial blood pressure observed after buprenorphine administration was primarily attributable to an increase in CI since SVR remained unchanged.

Although the changes in arterial pH may not be considered biologically relevant, as mean values remained within the reference range for horses (pH, 7.35 to 7.46), the increase in this variable after buprenorphine administration was coincident with a significant increase in RR. These changes, coupled with a slightly lower PaCO₂ after buprenorphine administration, suggest that alveolar ventilation was slightly increased.
Although μ opioid agonists cause an increase in intestinal smooth muscle tone, the sequential mechanical events that are responsible for propulsive motility are actually inhibited and the end result is constipation.\(^1,3,22\) Therefore, pure μ agonists such as morphine are more likely to cause constipation and gastrointestinal motility disturbances than butorphanol, which acts as a μ antagonist and a κ agonist drug.\(^22\) In a recent study,\(^23\) a continuous IV infusion regimen of butorphanol maintained for 24 hours (0.0027 mg/kg/h) resulted in less interference with abdominal auscultation scores than a single bolus of butorphanol (0.1 mg/kg) and the mean intestinal transit time did not differ from the control level in either regimen. Although morphine appears to be a good analgesic for superficial pain (eg, musculoskeletal pain), its use is controversial in horses.\(^19,25\) Data from 2 recent retrospective studies\(^24,25\) evaluating the incidence of postoperative complications in horses had different conclusions. One study\(^24\) evaluating the incidence of adverse effects associated with the intraoperative use of morphine in horses reported that a single dose of this opioid (0.1 to 0.17 mg/kg, IV) did not result in increased risk of adverse effects during the first 4 days after anesthesia. On the other hand, another large-scale retrospective study\(^25\) reported a 4-fold increase in the risk of colic in horses receiving morphine, compared with horses receiving no opioid agent or receiving butorphanol. However, factors such as stress caused by hospitalization, change in diet, and postoperative pain may also be implicated in motility disturbances in the postanesthetic period and represent possible confounding factors.

In rats, buprenorphine caused less pronounced reduction in gastrointestinal motility than morphine.\(^26\) In our study, abdominal auscultation scores decreased for 4 hours after buprenorphine administration, which is an expected effect of opioids in horses. Although auscultation of intestinal sounds is a somewhat subjective variable, this method has been validated in other studies and is considered a clinically useful tool to assess the effects of drugs or pathologic conditions on gastrointestinal motility.\(^11\) By use of a similar scoring system, the anticholinergic glycopyrrolate, a drug known for its gastrointestinal motility depressant effects, caused dose-dependent decreases in intestinal borborygmi.\(^27\) In that study, while a dose of 5 μg/kg of glycopyrrolate decreased intestinal sounds for approximately 4 hours after drug injection, a dose of 10 μg/kg decreased this variable from baseline conditions for a more prolonged period (18 hours) and caused signs of colic in 2 of 5 horses.\(^27\) Postoperative colic may represent a potential adverse effect observed after elective surgical procedures, even in horses not receiving opioids or other motility depressant drugs such as anticholinergics.\(^27\)

In summary, the use of buprenorphine induced excitation and stimulation of the hemodynamic function with minimal changes in arterial blood gas tensions. The excitatory phenomenon appears to substantially impact the clinical use of this drug, especially when used alone in pain-free horses. Further studies are required to evaluate the analgesic efficacy of buprenorphine as well as the clinical relevance of the undesirable adverse effects, such as decreased gastrointestinal motility and excitement.

References

phanol, flunixin, levorphanol, morphine, and xylazine in ponies. 


