Pharmacokinetics and adverse effects of butorphanol administered by single intravenous injection or continuous intravenous infusion in horses

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**Objective**—To determine an infusion rate of butorphanol tartrate in horses that would maintain therapeutic plasma drug concentrations while minimizing development of adverse behavioral and gastrointestinal tract effects.

**Animals**—10 healthy adult horses.

**Procedure**—Plasma butorphanol concentrations were determined by use of high-performance liquid chromatography following administration of butorphanol by single IV injection (0.1 to 0.13 mg/kg of body weight) or continuous IV infusion (loading dose, 17.8 µg/kg; infusion dosage, 23.7 µg/kg/h for 24 hours). Pharmacokinetic variables were calculated, and changes in physical examination data, gastrointestinal tract transit time, and behavior were determined over time.

**Results**—A single IV injection of butorphanol was associated with adverse behavioral and gastrointestinal tract effects including ataxia, decreased borborygmi, and decreased defecation. Elimination half-life of butorphanol was brief (44.37 minutes). Adverse gastrointestinal tract effects were less apparent during continuous 24-hour infusion of butorphanol at a dosage that resulted in a mean plasma concentration of 29 ng/ml, compared with effects after a single IV injection. No adverse behavioral effects were observed during or after continuous infusion.

**Conclusions and Clinical Relevance**—Continuous IV infusion of butorphanol for 24 hours maintained plasma butorphanol concentrations within a range associated with analgesia. Adverse behavioral and gastrointestinal tract effects were minimized during infusion, compared with a single injection of butorphanol. Continuous infusion of butorphanol may be a useful treatment to induce analgesia in horses. (Am J Vet Res 2001;62:183–189)

Nonsteroidal anti-inflammatory drugs (NSAID) such as flunixin and phenylbutazone are the most commonly used analgesic agents in horses. Their primary mechanism of action is inhibition of prostaglandin synthesis at sites of inflammation. Because of the potentially serious adverse effects of NSAID in horses, many clinicians attempt to minimize the dose administered, possibly at the expense of maintaining adequate analgesia. Opiate analgesics, which act centrally or at various levels of the spinal cord, are frequently used in other species for management of postoperative pain. The most common of these (eg, morphine, oxymorphone, fentanyl) are rarely used in horses because of adverse behavioral and gastrointestinal tract effects. A combination of opiates and NSAID probably achieves greater pain relief postoperatively than either medication alone. Combination drug therapy has the additional benefit of minimizing the risk of adverse effects from either class of drugs, because lower doses of each drug can be administered.

Butorphanol is a narcotic agonist-antagonist (ie, μ-receptor agonist and κ-receptor agonist) that is often administered to horses. Butorphanol ameliorates signs of superficial and visceral pain in horses when administered as a bolus IV injection but is effective for only 30 to 90 minutes. Intraoperative administration of butorphanol decreases clinical signs of postoperative pain in horses undergoing orthopedic surgery.

Unlike NSAID, analgesia induced by opioids correlates well with plasma concentrations of the drug. A bolus IV injection of butorphanol at the maximum label dose (0.1 mg/kg of body weight) may result in excitatory locomotor effects (eg, pacing) in clinically normal horses. It may also have adverse effects on gastrointestinal tract motility in these horses, although there is no decrease in gastrointestinal transit time. Because of these adverse effects and its brief duration of action, butorphanol is rarely administered to horses at maximum label doses and is most commonly used in combination with α2-agonists for short-term sedation and analgesia.

In humans, continuous IV infusion of narcotic analgesics is effective for control of postoperative pain. Continuous IV infusions are easy to administer and result in blood drug concentrations that can be maintained within a therapeutic range. The purpose of the study reported here was to determine an infusion rate of butorphanol tartrate in horses that would maintain therapeutic plasma drug concentrations while minimizing development of adverse behavioral and gastrointestinal tract effects.
Materials and Methods

Animals—Ten (4 castrated males and 6 females) healthy adult horses were used for this study. Several horses were used for more than 1 experiment. Horses were housed in box stalls and allowed free access to grass hay throughout treatment and observation periods in each experiment. Between treatments and experiments, horses were turned out on grass pasture. All experimental protocols were approved by the North Carolina State University Institutional Animal Care and Use Committee.

Study design—In experiment 1, a 2-way crossover trial was performed with 7 horses to determine the effects of IV administration of butorphanol. Horses were treated with butorphanol (0.1 to 0.13 mg/kg) or an equivalent volume of saline (0.9% NaCl) solution with a 3-week washout period between treatments. Initial treatments were determined randomly by a technical assistant; that individual did not participate in subsequent evaluation of the horses.

A catheter was placed in each jugular vein. Butorphanol or saline solution was administered through the catheter placed in the right jugular vein, and the catheter was immediately removed. Blood samples were collected from the left jugular vein catheter by aspiration with a syringe prior to (time 0) and 5, 10, and 20 minutes and 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, and 36 hours following treatment. Blood samples were immediately injected into a heparinized glass tube and stored on ice until centrifuged for collection of plasma. Plasma was stored at −70 C until butorphanol concentrations were measured. Physical examination data were recorded for each horse immediately prior to (time 0) and 5, 10, and 20 minutes and 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, and 36 hours following treatment.

In experiment 2, a 2-way crossover trial was performed with 5 horses to determine the effects of a continuous IV butorphanol infusion. Butorphanol or an equivalent volume of lactated Ringer’s solution (LRS) was administered as a continuous IV infusion with a 3-week washout period between treatments.

Visceral analgesia lasts for up to 4 hours in horses following IV administration of butorphanol at doses from 0.1 to 0.2 mg/kg. In experiment 1, mean plasma concentration of butorphanol 1 hour after butorphanol administration was approximately 20 to 30 ng/ml; this plasma concentration was selected as a target plasma concentration in experiment 2. To calculate a loading dose and infusion rate for the horses in experiment 2, systemic clearance and volume of distribution of butorphanol were determined in an initial pilot study involving 3 horses. These initial estimates were used to calculate appropriate dosages to maintain plasma butorphanol concentration at approximately 25 ng/ml. The loading dose (D₀) was calculated according to the formula:

\[ D₀ = C₂ \times V₀ \]

where C₂ is the desired plasma concentration, and V₀ is the apparent volume of distribution. The infusion rate (R₀) was calculated according to the formula:

\[ R₀ = C₀ \times D₀ \]

where C₀ is systemic clearance. From these calculations, the D₀, administered as a bolus IV injection, was 17.85 µg of butorphanol/kg. This was immediately followed by IV infusion of butorphanol at a rate of 23.7 µg/kg/h for 24 hours. Butorphanol was diluted in LRS so that the final infusion rate was approximately 4 ml/h. Control horses received an initial IV injection of an equivalent volume of saline solution followed by IV infusion of LRS at a rate of approximately 4 ml/h for 24 hours.

As in experiment 1, catheters were placed in both jugular veins. Butorphanol, saline solution, and LRS were administered through the catheter placed in the right jugular vein, and blood samples were collected from the left jugular vein. Heparinized blood samples and physical examination data were obtained from each horse immediately prior to (time 0) and 0.5, 1, 2, 3, 4, 8, 12, 16, 20, 24, 30, 36, and 42 hours after the initial bolus injection of butorphanol or saline solution. Researchers recording physical examination and behavioral data were masked to treatment.

Determination of plasma butorphanol concentrations—Butorphanol concentrations in plasma were measured by use of reverse-phase high-performance liquid chromatography (HPLC) with electrochemical (EC) detection. The buffer solution for the mobile phase was prepared by adding 3.854 g of ammonium acetate to 1.0 L of distilled water and adjusting the pH to 4.1 with glacial acetic acid. A 0.01M ammonium acetate solution was prepared for extraction steps by adding 0.771 g of ammonium acetate to 1.0 L of distilled water and adjusting the pH to 6.0. A butorphanol stock solution (1 mg/ml in methanol) was prepared from butorphanol tartrate. The stock solution was diluted in a methanol:water (50:50) solution for preparation of calibration standards. Diluted butorphanol was added to plasma, and 8 calibration standards (7.8 to 1,000 ng of butorphanol/ml of plasma) were used to obtain a calibration curve.

Plasma samples and calibration standards were prepared for HPLC, using solid-phase liquid extraction. Solid-phase extraction cartridges were prepared on a vacuum manifold. Cartridges were first conditioned with 2.0 ml of methanol, followed by 2.0 ml of 0.01M ammonium acetate (pH 6.0). One milliliter of plasma or calibration standards was added to the cartridge and aspirated with a vacuum pressure of ~5 mm Hg. The cartridges were washed with 2.0 ml of 0.01M ammonium acetate and 2.0 ml of 100% acetoniitrile. Cartridges were air-dried in the manifold for 1 minute and the collection tubes discarded. Butorphanol was eluted with 2.0 ml of 1% triethylamine in acetoniitrile. The eluate was evaporated under a flow of nitrogen in a 45 C water bath for 15 to 20 minutes. Samples were reconstituted with 200 µl of the mobile phase and transferred to HPLC injection vials.

The mobile phase consisted of 25% acetoniitrile and 75% ammonium acetate buffer (pH 4.1) at a flow rate of 1.0 ml/min. A volume of 75 µl was injected onto a reverse-phase C-8 column maintained at 40 C from an autosampler, and chromatograms were processed and integrated with computer software. Butorphanol was detected electrochemically. The EC detector had potentials of +400 mV in the screening electrode, +650 mV in the detection electrode, and +700 mV in the guard electrode. The limit of quantitation (LOQ) was defined as the lowest concentration on the calibration curve that could be determined with an accuracy within 15% of the true value. A new calibration curve was used for samples analyzed each day.

Six replicates of calibration standards were analyzed to determine accuracy and precision of the HPLC assay. Accuracy (ie, the percentage of deviation from the true value) was 7.0, 5.7, and 8.8% for the 7.81, 31.25, and 125 ng/ml calibration standards, respectively. Precision (ie, the percentage of deviation from the mean) was 6.2, 9.2, and 7.2% for the 7.81, 31.25, and 125 ng/ml calibration standards, respectively. The LOQ was 7.8 ng/ml (0.0078 µg/ml), and the calibration curve was linear, with R² ≥ 0.99 for each day's analysis.

Pharmacokinetic calculations—Plasma concentrations of butorphanol after a single IV injection were analyzed, using a computer program. The appearance of the concentration versus time curve, graphed on a semilogarithmic scale, indicated that butorphanol behaved according to a 2-compartment model. However, because concentrations of
butorphanol were greater than the LOQ in only 4 samples for 4 of the 7 horses, it was not possible to model plasma concentrations by use of 2-compartment pharmacokinetic methods. A 2-compartment model with 4 terms requires at least 5 data points for modeling. Therefore, noncompartmental pharmacokinetic methods were used.

In the noncompartmental analysis, area under the plasma concentration versus time curve (AUC) was calculated by use of the trapezoidal method and the residual (terminal) area calculated as $C_n/K_e$ where $C_n$ is the concentration at the last time point, and $K_e$ is the terminal rate constant. After initial determination of AUC, other variables such as $V_	ext{ss}$, mean residence time and $C_	ext{ss}$, were calculated, using standard formulas.

From plasma concentrations of butorphanol determined after IV infusion, $C_b$ and $V_b$ were calculated, using a computer program. For this model, we assumed a first-compartment distribution and provided as input $D_t$, $R_e$, and initial estimates for $V_b$ and elimination rate determined from data collected in experiment 1. Formulas used to calculate these variables were as follows:

$$C_T = C_b + C_{IV}$$
$$C_b = (D_t/R_e) e^{-t/TINF}$$
$$C_{IV} = (D_t/TINF) X (1/(V_p X K_e)) e^{-t(T-TINF)}$$

where $C_T$ is the plasma concentration, $C_b$ is the concentration contributed by the D$_t$, $C_{IV}$ is the concentration contributed by the IV infusion, $T$ is time, $T_{INF}$ is the duration of infusion, and $T^*$ is $T$–$T_{INF}$ for $T > T_{INF}$ and 0 for $T < T_{INF}$.

Clearance was calculated as $Cl_S = K_e V_d$ and elimination half-life as 0.693/$K_e$.

$$\text{Mean auscultation scores decreased significantly from pretreatment values in butorphanol-treated horses} 20 \text{ and 60 minutes after treatment (Fig 2). Butor-}$$

### Results

Experiment 1—The mean plasma butorphanol concentration versus time curve was determined following a single IV injection of butorphanol at a dose of 0.1 to 0.13 mg/kg (Fig 1). Values for pharmacokinetic variables were also calculated (Table 1). Four of 7 horses developed gross behavioral disturbances immediately after butorphanol injection. Affected horses staggered and were ataxic for up to 20 minutes after injection. One of the horses originally included in experiment 1 developed guttural pouch disease with secondary dysphagia during the washout period. Physical examination data from this horse was not included in the final analysis. Mean heart and respiratory rates after butorphanol injection were not significantly different, compared with pretreatment values. In addition, heart and respiratory rates in butorphanol-treated horses were not different from values for control horses at any time after treatment.

Mean auscultation scores decreased significantly from pretreatment values in butorphanol-treated horses 20 and 60 minutes after treatment (Fig 2). Butor-

<table>
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<th>Variable</th>
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<td>$C_{max}$ (ng/ml)</td>
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<td>0.475</td>
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$C_{max}$ = Maximum plasma concentration, $K_e$ = Elimination rate constant, $T_{2/3}K_e$ = Elimination half-life, $AUC_{0}^{\text{g}}$ = Area under the concentration versus time curve from time 0 to the final time point, $AUC_{\text{ss}}$ = Area under the concentration versus time curve from time 0 to infinity, $V_{DSS}$ = Volume of distribution determined by use of the area method, $C_{LOQ}$ = Total systemic clearance, $AUMC_{ss}$ = Area under the moment curve from time 0 to infinity, $MRT$ = Mean retention time, $V_{DSS}$ = Volume of distribution at steady state.

Figure 1—Mean (± SEM) plasma butorphanol concentrations in 7 horses before (time 0) and after IV administration of a single dose of butorphanol tartrate (0.1 to 0.13 mg/kg of body weight) to 7 adult horses.

By Dunnett test for multiple comparisons to pretreatment (time 0) values. Physical examination data were compared between butorphanol-treated and control groups by use of Student paired t-tests. Mean PEG transit time and area under the PEG concentration versus time curve were also compared between groups by use of Student paired t-tests. For all analyses, $P < 0.05$ was considered significant.
Phenol-treated horses passed significantly fewer fecal piles (mean ± SD, 8.6 ± 1.1 piles) in the first 24 hours after treatment, compared with control horses (11.4 ± 1.5 piles). However, the total number of fecal piles passed during the 48-hour observation period was not significantly different between treated and control groups (treated, 17.2 ± 1.5 piles; control, 20.2 ± 4.7 piles). Time to passage of first feces after treatment was significantly different between the 2 groups (treated, 2.8 ± 0.8 hours; control, 0.93 ± 1.0 hours). Fecal PEG concentrations and area under the PEG concentration versus time curve were not significantly different between groups (Fig 3).

Experiment 2—The mean plasma butorphanol concentration versus time curve was determined during continuous IV infusion of butorphanol (Fig 4). Mean (± SEM) plasma butorphanol concentration for all horses at all times during the 24-hour infusion was 26.34 ± 16 ng/ml (range, 4.64 to 68.3 ng/ml). Mean Vd (1.1 ± 1.6 L/kg), Cls (18.5 ± 9.7 ml/kg/min), and half-life (34 ± 38 minutes) were more variable, as indicated by the high SEM, compared with values determined after a single IV injection.

No adverse behavioral effects were detected in any horse in experiment 2. Mean heart and respiratory rates were not significantly different between treated and control groups at any time during or after administration of butorphanol.

Auscultation scores determined after IV infusion of butorphanol were not significantly different from pretreatment scores; mean scores ranged from 2.5 to 4. Butorphanol-treated horses passed significantly fewer fecal piles than control horses in the first 6 hours, first 24 hours, and throughout the observation period (Fig 5). Number of fecal piles passed between 24 and 48 hours (ie, after butorphanol infusion) was not significantly different between groups. At 18 hours, butorphanol-treated horses had a lower fecal concentration of PEG, compared with control horses, but this...
Antagonist. Administration of butorphanol (0.1 mg/kg, IV) decreased jejunal propulsive motility in ponies but did not affect pelvic flexure motility. In another study, this dose of butorphanol, as opposed to morphine, did not decrease total gastrointestinal transit time, intestinal borborygmi, or time to first defecation. In a toxicity trial in which butorphanol (1.0 mg/kg, IV, q 4 h) was administered to 2 horses for 4 days, both horses developed decreased abdominal borborygmi. Fecal production was markedly decreased in 1 horse, to the extent that mild abdominal discomfort developed after the drug was discontinued.

Adverse behavioral effects of butorphanol are much less severe, compared with morphine or fentanyl, and include ataxia and stimulation of locomotor activity. Effects are transient and dose-related and are most likely observed following bolus IV injection of high doses (0.1 to 0.5 mg/kg). Drug tolerance, with a diminution of adverse behavioral effects over time, may develop in horses given high doses of butorphanol for prolonged periods.

Butorphanol pharmacokinetics after IV injection in humans follow a 2-compartment model. The drug is extensively metabolized in the liver, with only 4 to 5% excreted unchanged in the urine. Metabolites have no known biological activity and are largely excreted in the urine; only 15% of metabolites are excreted via bile.

Results of the present study indicated that the terminal half-life of butorphanol in horses after a single IV injection was brief (44 minutes), and clearance was rapid (21 ml/kg/min). Volume of distribution (> 1.0 L/kg) indicated a wide distribution to tissues, which is typical for opiates. To obtain a desired plasma concentration for analgesia and avoid development of adverse effects, we estimated that the plasma concentration should be between 20 and 30 ng/ml. This range was selected because results of previous reports suggest that treatment of horses with butorphanol at 0.1 mg/kg induces analgesia for approximately 1 hour. In our study, plasma concentration of butorphanol 1 hour after IV administration of a single dose to most horses was 20 to 30 ng/ml (mean, 24.8 ng/ml). Therefore, the desired steady-state plasma concentration for the 24-hour infusion experiment was set at 25 ng/ml. The infusion rate necessary to maintain plasma concentrations in this range was calculated from V₀ and Clₜ determined during a pilot study of 3 horses. Mean (± SEM) plasma concentration for all times during the 24-hour infusion was 26.3 ± 16.2 ng/ml, indicating close agreement between desired and actual concentrations.

Although data collected during the 24-hour infusion experiment were more variable than during the single dose experiment, there was close agreement between mean systemic clearances of butorphanol during each experiment (infusion, 18.5 ml/kg/min; single dose, 21 ml/kg/min). Volume of distribution (infusion, 1.1 L/kg; single dose, 1.0 L/kg) and terminal half-life (infusion, 34 minutes; single dose, 44 minutes) were also in agreement between the 2 experiments. These results suggest that there is little difference in pharmacokinetics of butorphanol when administered as a single dose or constant-rate infusion. Butorphanol infusion for several hours did not appear to alter hemodynamics to a large enough degree to affect V₀ and Clₜ. Thus, butorphanol...
infusion rates can be accurately estimated from pharmacokinetics determined after IV administration of a single dose of butorphanol to horses.

Adverse behavioral effects were observed in 4 of 7 horses that received a single IV injection of butorphanol at the maximum label dose (0.1 mg/kg). These horses staggered immediately or were ataxic for up to 20 minutes following injection. These types of reactions have been described in horses receiving opiate analgesics and were not surprising. Mean plasma butorphanol concentration 10 minutes after butorphanol injection was greater, but not significantly so, in horses that developed adverse effects, compared with horses that did not (117.1 ± 40.3 vs 73.0 ± 13.7 ng/ml). Horses with plasma butorphanol concentrations < 50 ng/ml rarely developed adverse behavioral effects, and adverse behavioral effects were not detected in horses that received a continuous infusion of butorphanol, despite plasma concentrations that occasionally exceeded 50 ng/ml.

Heart and respiratory rates did not change significantly after administration of butorphanol, either as a single IV injection or an IV infusion. This result is consistent with results of a previous report indicating that butorphanol does not significantly alter cardiorespiratory function in horses at doses as high as 0.4 mg/kg administered intravenously.9

Butorphanol significantly decreased abdominal auscultation score and number of fecal piles passed in horses that received a single IV injection. This is in contrast to results of a previous report of butorphanol administration in ponies.9 The effect observed in our study was transient, and the discrepancy in findings between studies may be attributable to a physiologic difference between ponies and horses or differences in times at which animals were evaluated. Total gastrointestinal transit time was not affected by butorphanol administration in either study. We did not detect signs of abdominal pain as a result of impaction in any of the horses, and total number of fecal piles over the entire observation period was not significantly different between treated and control horses.

Gastrointestinal auscultation scores did not vary significantly from pretreatment values either during or after continuous IV butorphanol infusions. However, number of fecal piles passed during the 24-hour treatment period was significantly less in butorphanol-treated horses, compared with controls. Gastrointestinal transit time was not significantly decreased in treated horses, compared with controls, but the lack of significance was likely the result of the small number of horses in each group.

Continuous infusion of butorphanol maintained plasma butorphanol concentrations in a range that should provide substantial visceral analgesia without development of overt adverse behavioral effects. The inhibitory effects of butorphanol on gastrointestinal tract function suggest that caution should be exercised in the use of this drug in horses with potential impactions. Continuous infusion of butorphanol had a less significant impact on gastrointestinal tract function (eg, no decrease in auscultation score but a decrease in number of fecal piles passed) than a single IV injection, but the effect lasted for a prolonged period. A lower rate of infusion may further ameliorate adverse gastrointestinal tract effects. Clinical use of the infusion protocol described in this report will require titration of the dose to optimize analgesia and minimize adverse gastrointestinal tract effects.

It is difficult to adequately control postoperative pain in any species.17,20 Veterinarians typically rely on gross behavioral changes in horses to indicate the need for analgesics. However, in humans, dogs, and rats, gross behavioral disturbances only become evident when pain is severe.27,26 Administering analgesics to horses following surgery only when behavioral signs of pain (eg, pawing, flank gestures, rolling) have developed guarantees that horses will be severely distressed during the postoperative period. In addition, treatment of severely distressed horses may be less effective, because analgesics are most beneficial when administered prior to the onset of clinical signs of pain.26 Administration of a continuous IV infusion of butorphanol during the immediate postoperative period in horses may be a useful treatment to alleviate pain while minimizing risks of adverse effects.

References


