# Interactions of morphine and isoflurane in horses

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**Objective**—To quantitate dose- and time-related magnitudes of interactive effects of morphine (MOR) and isoflurane (ISO) in horses and to characterize pharmacokinetics of MOR in plasma and the ventilatory response to MOR during administration of ISO.

**Animals**—6 adult horses.

**Procedure**—Horses were anesthetized 3 times to determine the minimum alveolar concentration (MAC) of ISO in $O_2$ and then to characterize the change in anesthetic requirement as defined by the alteration in ISO MAC following IV administration of saline (0.9% NaCl) solution and 2 doses of MOR (low dose, 0.25 mg/kg; high dose, 2.0 mg/kg). Arterial blood samples were obtained before and after MOR and analyzed.

**Results**—Mean ± SD baseline ISO MAC was 1.43 ± 0.06%. The ISO MAC did not change with time after administration of saline solution. Effects of MOR on ISO MAC varied. Maximal change in MAC ranged from –20.2 to +28.3% and –18.9 to +56.2% after low and high doses of MOR, respectively. Typical half-life of MOR in plasma was 40 to 60 minutes and related to dose. Mean $Paco_2$ increased from 70 mm Hg before MOR to 88 to 102 mm Hg for 30 to 240 minutes after the high dose of MOR. Recovery from anesthesia after administration of the high dose of MOR was considered undesirable and dangerous.

**Conclusions and Clinical Relevance**—Our results do not support routine clinical use of MOR administered IV at dosages of 0.25 or 2.0 mg/kg as an adjuvant to anesthesia in horses administered ISO. (*Am J Vet Res* 2003;64:166–175)

Opioid drugs are widely used as primary and supplementary agents in the anesthetic management of humans and some other animals, especially those with minimal functional reserves of the circulatory system. An important characteristic of opioids that encourages this general approach is their ability to cause profound analgesia with comparatively little or no direct myocardial depression. Drugs of this class are frequently used in combination with inhalation anesthetics, and because of their analgesic potency, they permit reduction of the dose of inhalation anesthetic otherwise required.[1-5] Reduction of the dose of inhalation anesthetic generally promotes further cardiovascular stability and improved perianesthetic care.

Risk of general anesthesia continues to be a major factor when weighing the benefits for surgery in horses. Because of the substantial positive contributions from the use of opioids to improve anesthetic management of humans and dogs, it is natural to consider direct application of this knowledge to horses. Interspecies variations in responses to opioids may influence this decision. For example, it is widely appreciated that many horses have undesirable and even dangerous behavioral actions following opioid administration.[6-11] In addition, results of the limited number of pertinent studies[12-15] of opioid-inhalation anesthetic interactions in horses and ponies do not provide strong evidence in support of consistent, effective contributions from the use of opioids to improve anesthetic management of horses. Accordingly, additional study of the effectiveness of opioids as adjuvants in the anesthetic management of horses is necessary to support or refute common use in this species.

The primary objective of the study reported here was to determine the magnitude and duration of effect after IV administration of **morphine (MOR)**, a drug that is long regarded as the standard to which other opioid agonists are compared, on the **minimal alveolar concentration (MAC)** of **isoflurane (ISO)** that prevented purposeful movements in response to noxious stimulus in horses. In this study, we used techniques similar to those that we have used before to characterize MOR action in dogs, rhesus monkeys, and pigs.[5] The kinetics of MOR in plasma of horses during administration of ISO and the change in ventilation (as reflected by changes in $Paco_2$) associated with MOR administration in horses were determined. This approach allowed us to provide information on MOR action in horses and also permitted close indirect comparison of data derived from horses with data derived in a similar manner from other species.

## Materials and Methods

**Horses**—Six healthy unmedicated horses (5 Thoroughbreds, 1 Quarter Horse) that weighed (mean ± SE) 481 ± 12 kg were obtained for use in the study. Horses comprised 2 females and 4 castrated males and were 4.0 ± 0.6 years old. The study protocol was approved by the Animal Use and Care Administrative Advisory Committee of the University of California at Davis.

**Study conditions**—The 6 horses were each anesthetized 3 times with ISO to characterize the anesthetic-sparing effect of IV administration of saline (0.9% NaCl) solution and 2 doses of MOR (low dose, 0.25 mg/kg; high dose, 2.0 mg/kg). We chose the low dose of MOR to represent a moderate clin-

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ical dose and one that is within the dose range studied in unanesthetized horses.[7,16,17] The high dose of MOR was chosen on the basis of another study[5] and with the belief that results would define circumstances considered at an extreme of clinical use but within the range of published data from awake horses.[7]

**Procedure**—A crossover design was used. An equal number of horses (n = 3/group) were randomly assigned to receive saline treatment or the low dose of MOR during the first anesthetic episode. At least 3 weeks were allowed to elapse, and saline or low-dose MOR treatment for the horses was reversed during the second anesthetic episode. Two to 4 months after completion of the saline and low-dose MOR treatments, all 6 horses were again anesthetized, and the high dose of MOR was administered. Admittedly, this protocol created a potential for confounding on the basis of dose-order effects. Nevertheless, it was chosen because of the concern that the high dose of MOR could be associated with an increased risk of injury during recovery, which would prevent completion of the experiments in all 6 horses.

Feed was withheld from horses for 12 hours before induction of anesthesia, but water was always available. Anesthesia was induced in nonmedicated horses by administration of ISO in $O_2$, as described elsewhere.[18-20] Isoflurane was delivered to each horse via a mask connected to a large animal anesthetic circle system. Orotracheal intubation (cuffed endotracheal tube; internal diameter, 30 mm) was performed when anesthetic depth was suitable (within 10 to 15 minutes after the first breath of ISO). Following intubation, horses were positioned in left lateral recumbency on a thick foam-padded cart and transported to the laboratory (transportation period was 1 to 2 minutes) without being disconnected from the breathing circuit. After arriving in the laboratory, each horse was prepared for routine anesthetic monitoring during the remainder of the first hour of anesthesia. We used techniques that have been described elsewhere for our laboratory group.[19,21] Briefly, a base-apex lead ECG[a] was used to monitor **heart rate (HR)** and rhythm. An 18-gauge 2-inch catheter was inserted percutaneously into the right carotid artery, which had been surgically elevated to a position just beneath the skin during the months preceding the study. This catheter was connected to a strain gauge that was calibrated at the beginning of each experimental day by use of a mercury column. The calibrated strain gauge was then used to record **systolic blood pressure (SAP)** and **diastolic blood pressure (DAP)**; **mean arterial blood pressure (MAP)** was obtained by electronic dampening of the blood pressure signal. During recording, the strain gauge was positioned level with the sternum. A calibrated thermistor probe[b] was positioned in the nasopharynx to measure body temperature. Lactated Ringer's solution was infused at a rate of 2 to 4 mL/kg/h via a catheter placed in the left medial saphenous vein. The urinary bladder was catheterized, and the catheter was connected to a receptacle to permit continuous drainage and thereby avoid bladder distention and any associated influence on recovery from anesthesia.

End-expired gas samples were obtained by intermittent manual collection from a nylon catheter positioned near the caudal tip of the tracheal tube. Isoflurane was measured by use of an infrared gas analyzer[c] that was calibrated before the start of each experiment against multiple tank standards.[d] Calibration checks were also made throughout the day of each experiment. Concentrations of $O_2$ and $CO_2$ were also intermittently monitored by use of calibrated polarographic[e] and infrared[f] analyzers, respectively.

Horses were allowed to breath spontaneously, except for periodic (approx every 15 minutes) deep sighs accomplished by compression of the breathing circuit reservoir bag to a peak inspiratory airway pressure of 30 cm $H_2O$. **Respiratory rate (f)** was counted by visual observation of the rebreathing bag or tidal excursions of the chest.[19]

**Determination of MAC**—Standard techniques were used to determine MAC.[18] End-tidal ISO concentration was maintained constant for at least 20 minutes. Stepwise changes in ISO concentration were approximately 10% but not more than 20% of the previous concentration. A response was judged as positive when some purposeful movement (usually lifting or twisting of the head or movement of limbs) was detected during application (up to 60 seconds) of electrical stimulation of oral mucous membranes (50 V, 5 Hz, duration of 10 milliseconds). The MAC was determined in each horse in triplicate, and the mean value was considered to be the baseline (prior to MOR) value.

After completing baseline measurements, saline solution or MOR was injected IV during a 1-minute period, and MAC was determined multiple times during the next 4 to 5 hours. To accomplish this, the aforementioned technique used to determine MAC was modified in accordance with techniques reported elsewhere.[3,5,22] However, because of the behavior of horses in response to opioid injections, further modification of the technique was required soon after starting these experiments. In the study reported here, we injected MOR, but ISO concentration was not altered as in our previous studies of anesthetic adjuvant drugs. At approximately 10 minutes after MOR injection, we briefly (ie, a few seconds) applied a noxious stimulus and then observed the behavior of the horse. Response or lack of response of the horse then guided our decision to change or maintain the ISO concentration. When change of the ISO concentration was warranted, the response or lack of response determined whether we would increase or decrease the ISO concentration. We then waited at least 20 minutes before exposing the horse to the noxious stimulation again, such that our first postadministration test was most likely performed at a time when the plasma concentration of MOR was changing less rapidly (ie, after the pharmacokinetic phase of rapid redistribution of MOR). After we changed ISO concentration at other times, the new concentration was usually maintained constant for a period of 20 minutes before response to noxious stimulus was again evaluated. This waiting interval was used to minimize any alveolar-arterial anesthetic differences. When a positive response followed noxious stimulation, the end-expired ISO concentration was increased as rapidly as possible to a new concentration that was expected to result in a negative response. The new concentration was maintained constant until a positive response was again obtained, and the process was then repeated. In this phase of the study, the noxious stimulus was applied approximately every 20 minutes unless the horse's behavior to a stimulus predicted a closely pending positive response. In such cases (but assuming at least 20 minutes of constant conditions at this ISO concentration), noxious stimulation was reapplied at intervals of 5 to 10 minutes to improve precision in the measurement of timing of events. At each new end-expired ISO concentration, the mean time of the last minute for which a negative response was obtained and the time of purposeful movement in response to noxious stimulation were calculated. Usually 4 or more MAC data points were obtained from each horse following injection of saline solution or MOR.

**Cardiopulmonary measurements**—Values for HR, SAP, MAP, DAP, and f were considered to be a reflection of cardiovascular and respiratory performance and were determined from recordings obtained 30 to 60 seconds before application of noxious stimulation. To minimize differences attributable to the effect of differing anesthetic doses, values were obtained at ISO concentrations representing positive and negative responses to noxious stimulation. Data for each

variable were summarized as the maximum and minimum response for each horse, MOR dose, and periods before and after injection of MOR. We considered the minimum-to-maximum response range to be a summary of the horse's response to circumstances (eg, MOR dose and period before and after MOR administration). Inspired $O_2$[e] and $CO_2$[f] concentrations and end-tidal concentration of $CO_2$[f] were similarly monitored and recorded to ensure adequacy and consistency of experimental conditions.

**Blood gas measurements**—Arterial blood samples were anaerobically collected in heparinized syringes from anesthetized horses before injection of saline solution or MOR (ie, at ISO MAC) and at 1, 3, 6, 12, 18, 30, 60, 90, 120, 150, 180, 210, and 240 minutes after saline solution or MOR injections. Samples were used within a few minutes after collection for measurement[g] of $Pa_{O_2}$, $Pa_{CO_2}$, and $pH_a$. Immediately before anesthetic induction and administration of the high dose of MOR, we also obtained arterial blood samples percutaneously from 5 of the 6 horses while they were standing quietly in their stall. All measured results were corrected on the basis of the horse's rectal (awake) or pharyngeal (anesthetized) temperature.

At the conclusion of the high-dose MOR experiment, we obtained an arterial blood sample from 2 horses and then administered naloxone (0.005 mg/kg, IV) while the horses were still anesthetized. Another arterial blood sample was obtained 5 minutes after administration of naloxone and used to characterize changes in $Pa_{CO_2}$ following naloxone injection. These 2 horses were then transported to a recovery stall and allowed to recover from anesthesia without further interventions that could have potentially modified behavior during recovery.

**Morphine measurements**—Heparinized arterial blood samples were obtained. Samples were centrifuged, and plasma was immediately harvested. Plasma samples were obtained immediately before and 3, 6, 12, 18, 21, 24, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes after MOR injection. Samples were immediately frozen and stored at −70°C until analyzed. Samples were assayed to determine free morphine content by use of radioimmunoassay, as described elsewhere.[5]

**Pharmacokinetic analysis**—Plasma MOR concentration-versus-time data obtained from each horse were analyzed by compartmental[h] and noncompartmental methods based on statistical moment theory.[5]

**Evaluation of recovery from anesthesia**—Horses were monitored during recovery from anesthesia, and several variables were monitored. A subjective, overall recovery score was assigned by 1 of the authors (EPS) for each horse at the conclusion of recovery from anesthesia. The score was based on a 4-point scale (0, poor; 1, fair; 2, good; 3, excellent) as determined on the basis of clinical judgment.

**Statistical analysis**—Data were grouped and values were expressed as the mean ± SE, except as indicated. One- and 2-way repeated-measures ANOVA tests were applied to the raw and logarithmically transformed cardiopulmonary and blood gas data, and the Tukey (all pairwise comparisons) or Dunnett (multiple pairwise comparisons vs baseline values) tests were applied, when appropriate, as post-hoc tests. When appropriate, nonparametric data were further analyzed by use of the Wilcoxon sign-rank test.[i] Initial analysis of data for the low-dose MOR and saline solution injections did not reveal an order effect, so an assumption was made that there was not an order effect associated with the data for the high-dose MOR injection, and the data from the 3 dose conditions were analyzed collectively. Occasionally, a paired Student t-test was used to compare selected values with results of baseline measurements. A paired Student *t*-test was also used to determine significance for the dose of MOR on major pharmacokinetic variables describing disposition of the drug. Perianesthetic data obtained prior to injection of MOR were considered baseline values for the blood gas analyses. A value of $P < 0.05$ was considered significant.

## Results

**ISO MAC and morphine-induced changes in ISO MAC**—Baseline ISO MAC in $O_2$ determined by averaging results for each of the 6 horses for each of the 3 anesthetic episodes was 1.43 ± 0.06% (range, 1.20 to 1.93%). Body temperature at MAC was 37.6 ± 0.1°C (range, 36.9 to 38.3°C). Results for each experimental grouping were summarized (**Table 1**). Baseline MAC did not differ among the 3 test groupings. The ISO MAC did not change with time when horses were administered saline solution (**Fig 1**). We also did not detect a difference in MAC measured before MOR injection and results obtained within the first hour after MOR injection for either dose of MOR. However, although the net change in MAC did not differ significantly before and after MOR injection, a qualitative peak directional change in MAC (ie, an increase or a decrease in MAC) of ≥ 10% was detected for specific

Table 1—Mean ± SE values for changes in minimum alveolar concentration (MAC) of isoflurane before and after IV injection of saline (0.9% NaCl) solution or 2 doses of morphine (MOR) in 6 horses

| | | | Initial change in MAC after IV injection† | |
|---|---|---|---|---|
| Injection | Baseline MAC*at | Temperature MAC (°C) | Time (min) | Increase in MAC (%) |
| Saline solution | 1.46 ± 0.12 | 37.5 ± 0.2 | NC | NC |
| MOR (0.25 mg/kg) | 1.44 ± 0.10 | 37.6 ± 0.2 | 36 ± 4 | 5.4 ± 7.5‡ |
| MOR (2.0 mg/kg) | 1.40 ± 0.09 | 37.7 ± 0.2 | 40 ± 3 | 11.2 ± 12.5 |

*Values for MAC are expressed as volumes percentage of end-expired isoflurane. †Defined as > 5% change (positive or negative) from baseline MAC within 1 hour after IV injection; represents values obtained for only 5 horses. ‡A bidirectional change was observed in 2 horses, so the predominant directional change observed is reported.
NC = No change.

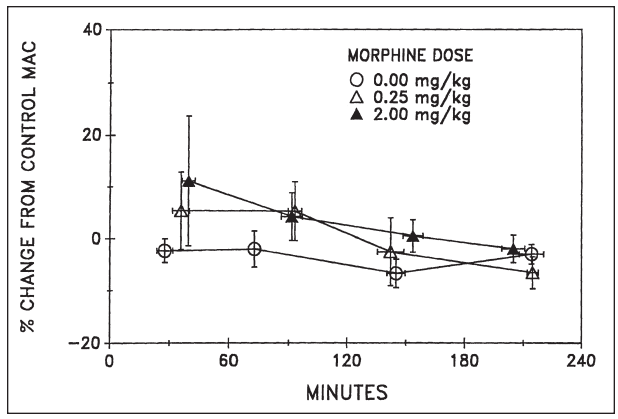


Figure 1—Time-related responses in change of minimum alveolar concentration (MAC) of isoflurane following IV injection of saline (0.9% NaCl) solution (open circle), a low dose of morphine (0.25 mg/kg; open triangle), and a high dose of morphine (2 mg/kg; solid triangle). Values reported are mean ± SE. Time 0 = Start of IV injection.

horses. Injection of the low dose of MOR caused an increase in MAC of ≥ 10% in 3 of 6 horses, a decrease in MAC in 1 horse, and no change in MAC (ie, values differed by < 10% from baseline MAC) in the remaining 2 horses. Maximal change in MAC following the low dose of MOR ranged from –20.2 to +28.3%.

Following administration of the high dose of MOR, MAC increased ≥ 10% in 4 horses, decreased in 1 horse, and did not change in the remaining horse. Range of maximal change in MAC measured after the high dose of MOR was –18.9 to +56.2%. Two horses had extreme responses (**Fig 2**). The data from all 6 horses were graphically summarized (Fig 1). Results obtained after IV injection of 2.0 mg of MOR/kg in the horses of this study were graphically compared with data reported[5] by our laboratory group for dogs, rhesus monkeys, and miniature pigs treated in the same manner (**Fig 3**).

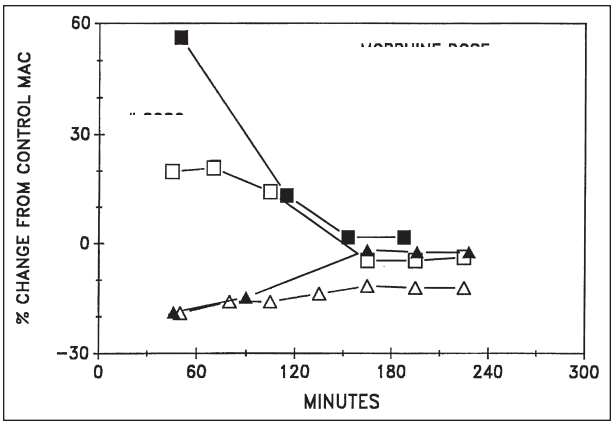


Figure 2—Interaction of morphine and isoflurane in the response of 2 horses (horse 1, square; horse 2, triangle) that represented the extremes of observed responses after IV administration of each dose of morphine (0.25 mg/kg, open symbols; 2 mg/kg, solid symbols). Time 0 = Start of IV injection.

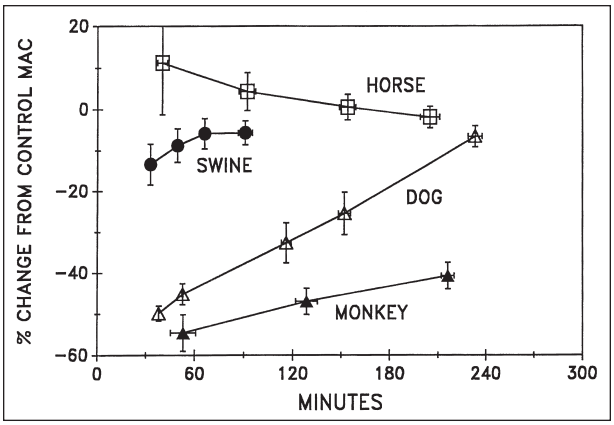


Figure 3—Time course for the change in isoflurane MAC accompanying a bolus injection of morphine (2 mg/kg, IV) in 6 horses of the study reported here and 6 dogs, 6 rhesus monkeys, and 6 miniature pigs from another report.[5] Values reported are mean ± SE. Time 0 = Start of IV injection.

**Cardiopulmonary responses**—The range of values for HR, SAP, DAP, MAP, and f before and after administration of saline solution, low-dose MOR, and high-dose MOR were determined (**Table 2**). We did not detect significant differences in results for any of the variables before injection of saline solution or MOR. Values after MOR injection were greater than before MOR injection within a treatment group, but there was no change in values before and after injection of saline solution. Maximum and minimum values for HR and blood pressures were significantly greater following injection of the high dose of MOR, compared with values after injection of saline solution or the low dose of MOR. The increase in HR following injection of the high dose of MOR was also maintained for a longer duration (most of the remainder of anesthesia), compared with values obtained following injection of the low dose of MOR (values often returned to baseline within 1 hour after MOR injection).

**Blood gas analysis**—Prior to injection of saline solution, $Pa_{O_2}$ and $Pa_{CO_2}$ were 294 ± 71 and 67.9 ± 5.5 mm Hg, respectively, and $pH_a$ was 7.342 ± 0.014. Pretreatment values did not differ significantly for the 3 treatments. The $Pa_{O_2}$ and $Pa_{CO_2}$ did not change significantly with time after injection of saline solution or the low dose of MOR (**Table 3**; **Fig 4**). The time-associated average $Pa_{O_2}$ following injection of saline solu-

Table 2—Mean ± SE values for cardiopulmonary variables in 6 isoflurane-anesthetized horses before and after IV injection of saline solution or 2 doses of MOR

| | | Saline solution | | MOR (0.25 mg/kg) | | MOR (2 mg/kg) | |
|---|---|---|---|---|---|---|---|
| **Variable** | **Range** | **Before** | **After** | **Before** | **After** | **Before** | **After** |
| HR (beats/min) | Maximum | 38.9 ± 3.0[a] | 42.2 ± 3.3[b,A] | 37.8 ± 0.7[a] | 51.4 ± 4.7[b,A] | 42.4 ± 3.9[a] | 70.0 ± 4.3[b,B] |
| | Minimum | 32.2 ± 2.4 | 36.7 ± 3.1[A] | 35.6 ± 1.6 | 38.0 ± 1.2[A] | 39.4 ± 3.0[a] | 54.8 ± 4.6[b,B] |
| SAP ( mm Hg) | Maximum | 117 ± 6[a] | 125 ± 5[b,A] | 124 ± 6 | 136 ± 3[A] | 130 ± 8[a] | 165 ± 5[b,B] |
| | Minimum | 104 ± 8 | 102 ± 6 | 105 ± 5 | 98 ± 2[A] | 112 ± 6 | 120 ± 5[B] |
| DAP (mm Hg) | Maximum | 78 ± 5 | 79 ± 4[A] | 83 ± 5 | 87 ± 4[A] | 82 ± 5[a] | 107 ± 5[b,B] |
| | Minimum | 59 ± 5 | 62 ± 4[A] | 65 ± 4 | 59 ± 2[A] | 70 ± 5 | 75 ± 4[B] |
| MAP (mm Hg) | Maximum | 91 ± 5 | 94 ± 4[A] | 96 ± 5 | 102 ± 3[A] | 98 ± 6[a] | 126 ± 4[b,B] |
| | Minimum | 77 ± 6 | 74 ± 5[A] | 90 ± 4 | 72 ± 2[A] | 84 ± 5 | 88 ± 5[B] |
| f (breaths/min) | Maximum | 4.8 ± 0.8 | 5.7 ± 0.7 | 6.2 ± 1.0 | 5.9 ± 0.4 | 5.8 ± 1.0 | 5.9 ± 1.3 |
| | Minimum | 3.7 ± 0.8 | 3.5 ± 0.9 | 3.9 ±1.1 | 2.6 ± 0.8 | 3.4 ± 1.0 | 2.6 ± 1.4 |

Anesthetic doses at all time points were approximately equipotent (ie, equivalent to 1.0 MAC for isoflurane in $O_2$ with isoflurane adjusted to balance time-related decay in plasma MOR concentrations).

[a,b]For each treatment, values within a row with different superscript letters differ significantly ($P < 0.05$) before and after IV administration. [A,B]Within a row, values with different superscript letters differ significantly ($P < 0.05$) among treatments.

HR = heart rate. SAP = Systolic arterial blood pressure. DAP = Diastolic arterial blood pressure. MAP = Mean arterial blood pressure. f = Respiratory rate.

tion ranged from a high of 327 mm Hg to a low of 243 mm Hg. Values for $Pa_{O_2}$ following injection of saline solution were larger but not significantly different from values at comparable times following injection of the low dose of MOR. For technical reasons, some time-associated blood gas values were not obtained after injection of saline solution. Consequently, statistical comparison of blood gas values measured after saline solution and after MOR was limited in scope and power.

Table 3—Mean ± SE values for $Pa_{O_2}$ and $Pa_{CO_2}$ before and after IV injection of 2 doses of MOR in 6 isoflurane-anesthetized horses

| | $Pa_{O_2}$ (mm Hg) | | $Pa_{CO_2}$ (mm Hg) | |
|---|---|---|---|---|
| **Time** | **0.25 mg/kg** | **2 mg/kg** | **0.25 mg/kg** | **2 mg/kg** |
| Before MOR | 288 ± 72 | 341 ± 39 | 71.1 ± 6.5 | 66.9 ± 3.6 |
| After MOR (min) | | | | |
| 1 | 312 ± 72 | 337 ± 51 | 65.2 ± 3.2 | 72.7 ± 5.6 |
| 3 | 272 ± 78 | 283 ± 53 | 70.8 ± 7.5 | 82.8 ± 6.2 |
| 6 | 245 ± 58 | 261 ± 32 | 76.6 ± 6.8 | 85.8 ± 6.8* |
| 12 | 230 ± 60 | 273 ± 44 | 81.1 ± 7.9 | 90.1 ± 9.7* |
| 18 | 240 ± 53 | 229 ± 39 | 73.6 ± 5.9 | 101.2 ± 8.8* |
| 30 | 224 ± 59 | 190 ± 48 | 76.3 ± 9.3 | 91.5 ± 6.6* |
| 60 | 194 ± 49 | 197 ± 56 | 74.6 ± 5.3 | 101.6 ± 5.7* |
| 120 | 153 ± 48 | 150 ± 35* | 79.6 ± 8.5 | 99.9 ± 8.4* |
| 150 | 176 ± 63 | 128 ± 31* | 74.1 ± 6.1 | 94.2 ± 9.0* |
| 180 | 164 ± 48† | 128 ± 36* | 87.3 ± 11.6† | 89.2 ± 9.8* |
| 210 | 215 ± 57† | 111 ± 25* | 68.9 ± 7.4† | 90.5 ± 11.2* |
| 240 | 179 ± 54† | 113 ± 20* | 75.8 ± 7.6† | 87.9 ± 10.9* |

*Within a column, value differs significantly ($P < 0.05$) from the value before MOR, as determined by use of repeated-measures ANOVA. †Represents results of only 4 horses.

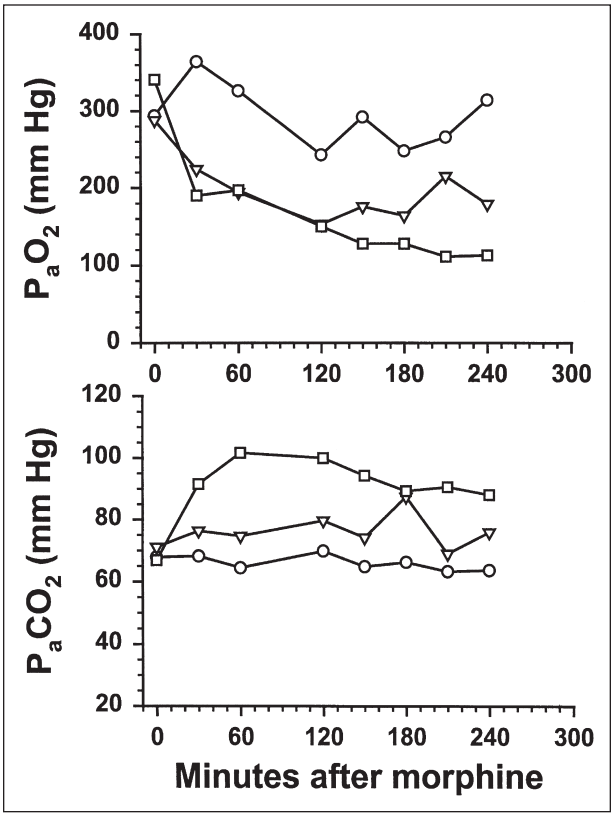


Figure 4—Time course for the change in $Pa_{O_2}$ and $Pa_{CO_2}$ before and after an IV bolus injection of saline solution (circle), a low dose of morphine (0.25 mg/kg; inverted triangle), or a high dose of morphine (2 mg/kg; square) in 6 horses anesthetized with isoflurane.

Values of $Pa_{CO_2}$ following injection of the low dose of MOR were larger but not significantly different from those following injection of saline solution. The $Pa_{CO_2}$ increased following injection of the high dose of MOR, whereas $Pa_{O_2}$ decreased. After injection of the high dose of MOR, mean values of $Pa_{O_2}$ and $Pa_{CO_2}$ differed significantly ($P < 0.001$ and $P = 0.006$, respectively) among specific time points after allowing for drug-dose considerations. Values for specific time points that differed significantly from values obtained prior to injection of MOR were determined by use of the Dunnett test (Table 3). Data obtained after injection of the high dose of MOR were graphically compared with data that were similarly derived from a study[5] of dogs, rhesus monkeys, and miniature pigs that received the same dose of MOR via IV administration (**Fig 5**).

Values for $pH_a$ changed in accordance with variations in $Pa_{CO_2}$. The calculated base balance was initially within the reference range[18,19,21] and did not change with time during the study. Accordingly, for simplicity, $pH_a$ and data for base balance were not included here.

Mean values for $Pa_{O_2}$ and $Pa_{CO_2}$ in the 5 horses tested immediately prior to anesthetic induction and in the high-dose MOR experiment were 103 ± 5 and 43.4 ± 1.4 mm Hg, respectively. Mean value for $pH_a$ in the 5 horses was 7.460 ± 0.013.

In the 2 horses administered naloxone prior to recovery (still anesthetized with a constant dose of ISO), mean $Pa_{CO_2}$ immediately before injection was 85 mm Hg. Five minutes after injection of naloxone, and without a change in ISO concentration, mean $Pa_{CO_2}$ in the 2 horses was 62 mm Hg.

**Plasma morphine analysis**—Pharmacokinetic variables for MOR representing various conditions of ISO anesthesia in the horses were determined (**Table 4**). Other than the half-life of MOR in plasma, which was significantly greater for the high dose of MOR, results of these calculated variables did not differ significantly on the basis of administered dose of MOR. The arterial plasma concentration-time pattern was best expressed as a biexponential function (**Fig 6**). The

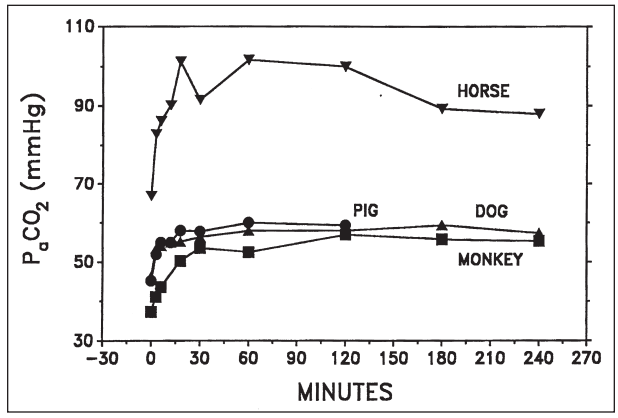


Figure 5—Values of $Pa_{CO_2}$ before and after administration of morphine (2 mg/kg, IV) in isoflurane-anesthetized animals (6 dogs, 6 rhesus monkeys, and 6 miniature pigs) from another report[5] and 6 horses of the study reported here. Time 0 = Start of IV injection.

coefficient of determination resulting from analysis of plasma MOR concentration versus time relationships for each horse ranged from 0.992 to 0.998.

**Recovery from anesthesia**—Total anesthesia time, defined as the time from a horse's first breath of ISO to the time the breathing circuit was disconnected from the endotracheal tube, was calculated (**Table 5**). Interval from the beginning of anesthetic exposure to the last MAC determination was 405 ± 13, 403 ± 18, and 484 ± 17 minutes when horses were injected with saline solution, low-dose MOR, and high-dose MOR, respectively. Mean time from last MAC determination to discontinuation of ISO and moving the horse to a recovery stall was 13 minutes. This difference was related to time needed for catheter removal and other management considerations prior to movement of the horse to a recovery stall. Overall duration of anesthesia associated with high-dose MOR was significantly longer (mean of 80 minutes longer) than the duration for saline solution and low-dose MOR; duration of anesthesia did not differ significantly for saline solution and low-dose MOR.

Horses administered saline solution or low-dose MOR had variable recovery behavior that was typical of horses recovering after 4 to 6 hours of inhalation anesthesia (Table 5). Most horses recovered reasonably well (but not flawlessly), and no major injuries were evident. In contrast, when horses were administered the high dose of MOR, all 6 had extremely difficult recoveries. Typically, the horses made strong, sometimes sustained, running or galloping movements while lying in lateral recumbency. During attempts to achieve sternal posture, they would bang or slap the sides of their heads on the floor of the recovery stall. Typically, an attempt to achieve sternal posture would result in 2 to 5 banging or slapping actions of the head before the horse would cease its efforts and lie quietly until the next attempt. Attempts to stand were usually extremely strong and determined. Standing occurred on the first or second attempt, despite the fact horses were ataxic once they stood. Once they had stabilized in a standing position, horses also characteristically began to pace (seemingly aimlessly) around the recovery stall and would not stop. The 2 horses that received naloxone 20 minutes prior to being moved to the recovery stall did not act noticeably different from the other 4 horses during their recovery. One horse was administered 400 mg of xylazine hydrochloride, IV, while still in lateral recumbency to stop the violent attempts to achieve sternal and standing postures. During much of the recovery period (ie, until leaving the recovery stall), HR of these horses typically was at least 40 to 60 beats/min, and f was in the range of 30 to 60 breaths/min.

After recovery, horses that had been administered saline solution or the low dose of MOR typically walked quietly back to their outdoor holding pen with little evidence of ataxia. On arrival in the pen, they immediately went to the fresh hay placed there for them and began to eat. In contrast, their behavior and actions differed noticeably after they had been administered the high dose of MOR. In this case, typical behavior was a spirited trot back to the outside holding pen with varying degrees of ataxia. Horses would occasionally bump into the person leading them to the pen as if they did not recognize that the person was there. Once in the pen, they would move around the pen at a trot or walking at a continual slow pace. They did not have an apparent desire to eat. When hay was offered by hand, the horses appeared indifferent. Horses that did accept it merely carried the hay in their mouth

Table 4—Mean ± SE values of selected pharmacokinetic variables for 2 doses of MOR after IV injection in 6 isoflurane-anesthetized horses

| Variable | MOR (0.25 mg/kg) | MOR (2 mg/kg) |
|---|---|---|
| $t_{1/2}$ (min) | 39.6 ± 1.9[a] | 59.8 ± 1.7[b] |
| $Vd_{ss}$ (mL/kg) | 1,219 ± 152 | 1,902 ± 292 |
| Cl (mL/min/kg) | 40.4 ± 3.8 | 39.0 ± 3.9 |
| $V_c$ (mL/kg) | 219 ± 35 | 277 ± 51 |

[a,b]Values with different superscript letters differ significantly ($P < 0.05$).
$t_{1/2}$ = Elimination half-life. $Vd_{ss}$ = Volume of distribution at steady state. Cl = Systemic clearance. $V_c$ = Apparent volume of central compartment.

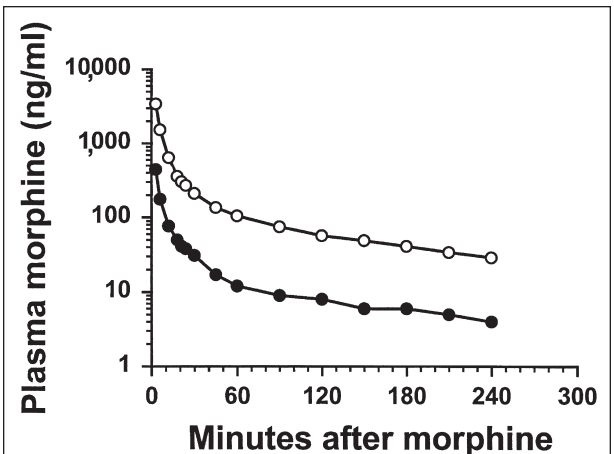


Figure 6—Plasma concentration of morphine plotted against time. Each line represents mean value of the pooled data for the 6 horses at the time points indicated after IV injection of a low dose of morphine (0.25 mg/kg; solid circle) and a high dose of morphine (2 mg/kg; open circle). Injections were administered during a period of 60 seconds. Time 0 = Start of IV injection.

Table 5—Mean ± SE values for characteristics of 6 isoflurane-anesthetized horses with and without IV administration of MOR

| Variable | Saline solution | MOR (0.25 mg/kg) | MOR (2 mg/kg) |
|---|---|---|---|
| Anesthesia time (min) | 418 ± 13[a] | 424 ± 13[a] | 494 ± 191[b] |
| Recovery time (min) | 33 ± 4 | 25 ± 5 | 32 ± 9 |
| Time to extubation (min) | 25 ± 4 | 20 ± 2 | 27 ± 4 |
| No. of attempts to attain sternal position | 3.5 ± 1.4 | 3.5 ± 0.4 | 4.8 ± 1.2 |
| No. of attempts to attain standing position | 2.3 ± 0.7 | 1.7 ± 0.5 | 1.5 ± 0.2 |
| Recovery score | 2.2 ± 0.2[a] | 1.7 ± 0.3[a] | 0.7 ± 0.3[b] |

Recovery score was assigned for each horse at the conclusion of recovery from anesthesia (0, poor; 1, fair; 2, good; and 3, excellent).
[a,b]Within a row, values with different superscript letters differ significantly ($P < 0.05$).
Anesthesia time = Time from a horse's first breath of isoflurane to the time the breathing circuit was disconnected from the endotracheal tube. Recovery time = Time from disconnection of the breathing circuit to the time the horse stood and remained standing. Time to extubation = Time from disconnection of the breathing circuit to the time when the endotracheal tube was removed.

while walking around the pen and did not attempt to chew or swallow it. Duration of this behavior was variable but lasted from 30 minutes to approximately 2 hours after returning to the pen. Walking movements gradually subsided, and horses appeared lethargic but did display some interest in the hay. Some of these horses still appeared slightly lethargic the next morning, but other complications were not evident then or subsequently.

## Discussion

Morphine is in general use as an anesthetic adjuvant, because it reduces the MAC (or median effective dose) for the accompanying inhalation anesthetic.[1,2,4,5,22,23] The primary object of the study reported here was to determine whether MOR administered in conjunction with ISO would result in improvements in anesthetic management of horses, compared with results for the use of ISO alone. Results of this study do not support the routine use of MOR as an anesthetic adjuvant in horses. Discussion of our results can be conveniently separated into 4 clinically important categories: MOR effect on ISO MAC, MOR effect on cardiovascular performance, MOR effect on ventilation, and MOR effect on recovery of horses from anesthesia maintained with ISO.

The MAC determined for ISO in $O_2$ in this study (1.43 ± 0.06%) was similar to that reported elsewhere for horses.[18] In addition, similar values have been reported in dogs[24] and are consistent with the authors' experiences with dogs and horses. The ISO MAC in the study reported here did not change with duration of anesthesia (Fig 1).

Injection of a low dose of MOR did not cause an appreciable change in MAC. The ISO MAC increased following injection of the high dose of MOR (peak change measured during the first hour of study was 11.2 ± 12.5%; Table 1) and then returned to baseline by approximately 2 to 3 hours after injection (Fig 1). These responses differ greatly from responses in 3 other species in a study[5] conducted in a similar manner by our laboratory group (Fig 3). However, our summarized results do not adequately convey other important and distinctive considerations. In contrast to our experience with other species, responses of specific horses after injection of MOR were much less consistent with regard to direction from baseline and magnitude (percentage) of change. Responses of these horses to MOR also contrasted markedly with responses reported when xylazine was used in similar conditions in another study.[25] For example, the response to injection of MOR by some horses was an increase in MAC, whereas other horses had a decrease in MAC, and still others had no change in MAC in response to MOR. In that other study,[25] MAC consistently decreased in response to xylazine. There were extremes of response to MOR (in directional change from baseline and magnitude of change) in the study reported here (Fig 2). In 1 horse, MAC decreased approximately 20% for each dose of MOR, whereas in another horse, MAC increased following each dose of MOR (by as much as 56% following the high dose). Retrospectively, we could not determine distinguishing characteristics that would have allowed us to identify beforehand those horses that would respond to MOR with an increase (or decrease) in ISO MAC.

It has been reported[11,16] that μ-opioid receptor agonists are able to induce small but measurable somatic analgesic responses in awake horses. In anesthetized animals, the magnitude of decrease in MAC of an inhalation anesthetic is commonly considered an indication of analgesic potency of an accompanying drug. Analysis of data in the study reported here suggested that injection of MOR (2 mg/kg, IV) is inconsistent and, in some cases, ineffective as a potent analgesic agent in horses (Fig 3). These data are consistent with results of another study[15] in which alfentanil (another μ-opioid) was administered to halothane-anesthetized horses and with conclusions reached by other researchers[26] following their analysis of investigations of a number of models for testing analgesic responses to MOR in awake horses. However, findings in the study reported here are in sharp contrast to results for similar experiments on dogs and nonhuman primates.[5]

Two additional considerations of the study reported here deserve mention. First, similar to another study,[15] the MAC technique may be unable to adequately discriminate between arousal of the CNS or stimulation and suppression of response to noxious stimulation (ie, analgesia). The behavioral end point for determining MAC is an all-or-nothing (movement or no-movement) response to a noxious stimulus. It is possible, although unlikely, that because of CNS stimulation caused by MOR, horses move in response to the electrical stimulus for a reason other than perception of pain. In addition or alternatively, the doses of MOR used in this study were below those necessary for use in the detection of analgesia by the anesthetic-sparing technique. Kamerling et al[26] have suggested that the analgesic effect of MOR in horses is substantially weaker than its behavioral (ie, CNS arousal) and cardiovascular effects.

Regardless of whether the analgesic potency of MOR is less in horses, compared with the potency in many other species, the increase in MAC (ie, need for additional inhalation anesthetic) associated with MOR administration before or during general anesthesia is an important practical consideration in the design of clinical anesthetic protocols, especially for such large and potentially volatile animals as horses. Consequently, the inconsistent and sometimes dramatic increase in ISO MAC accompanying MOR administration to ISO-anesthetized horses does not constitute a benefit, and therefore, does not support widespread addition of MOR to contemporary anesthetic protocols for use in horses.

Allowing for the influence of anesthetic dose and time of measurement and the fact that broad comparisons were made of differently summarized data, results of HR and arterial blood pressure measurements during only ISO anesthesia in the study reported here are comparable to results of other studies[18,19,21] of ISO by our laboratory group. Values within a variable grouping before injection of saline solution or MOR did not differ in this study. However, there were significant changes in SAP and HR following injection of saline

solution. These changes most likely represent normal variability and temporal influence[21] and, given the magnitude of difference, are not considered important within the realm of the study.

Maximum HRs were significantly increased following MOR injection. These findings are in contrast to the fact that HR decreased or did not change following administration of a similar dose of MOR in our study of dogs, monkeys, and pigs.[5] Changes in HR with an increase in blood pressure after injection of high-dose MOR in the study reported here are comparable to observations following administration of MOR in awake horses and presumably relate to CNS stimulation[16,17] and increased sympathetic tone. These results also lend support to comments of authors in a study[26] who indicated that the cardiovascular effects of MOR are stronger than its analgesic effects. In particular, HRs of the magnitude evident following injection of high-dose MOR in the study reported here would, as a general rule, be undesirable in clinical management of horses undergoing general anesthesia and surgery.

Values prior to injection of saline solution or MOR for $Pa_{O_2}$ and $Pa_{CO_2}$ reported here are similar to values reported for horses anesthetized with ISO but without other drugs.[18,19,21] Following injection of saline solution or the low dose of MOR, $Pa_{O_2}$ and $Pa_{CO_2}$ did not change significantly with time. Lack of change in $Pa_{CO_2}$ with time following injection of saline solution differs from results of other studies[21,27] of ISO anesthesia in which there were time-related effects in the form of a temporal increase in $Pa_{CO_2}$. The difference between results of the study reported here and those of other studies is likely a result of differences in methods used. For example, absolute ISO dose in the study reported here was less than that reported for temporal studies,[21,27] and the dose of ISO varied over time in this study, whereas the dose of ISO was held constant over time in the other studies.[21,27]

The IV injection of high-dose MOR caused a significant rapid increase in $Pa_{CO_2}$ (Table 3, Fig 4). The $Pa_{CO_2}$ increased 20 to 30 mm Hg following injection of MOR. The increase above values obtained prior to MOR injection was maintained for the remainder of the anesthetic period except in the 2 horses that were administered an opioid antagonist (ie, naloxone). In those 2 horses, $Pa_{CO_2}$ returned to values similar to those before MOR injection within 5 minutes after they received an injection of naloxone (0.005 mg/kg, IV). The direction of change in $Pa_{CO_2}$ following high-dose MOR in horses was the same as that seen in other species[5]; however, the magnitude of change and the degree of hypercapnia are in sharp contrast to those reported in dogs, monkeys, and pigs (Fig 5). The $Pa_{O_2}$ and $Pa_{CO_2}$ following injection of the low dose of MOR increased slightly but not significantly. Lack of significant change following injection of the low dose of MOR suggests the threshold for a hypercapnic effect was not reached in these horses. An alternative explanation is that the magnitude of increase was small and was overshadowed by frequent manipulation of ISO dose (and the associated effect on $Pa_{CO_2}$) necessary in these experiments (ie, actual effect was clouded by experimental noise). Furthermore, the likelihood of this possibility is improved when results during the period after injection of the low dose of MOR were compared with results following injection of saline solution (Fig 4).

Values of $Pa_{CO_2}$ in some horses were within the range that will decrease MAC in halothane-anesthetized dogs,[28] especially following injection of high-dose MOR. Values of $Pa_{CO_2} > 95$ mm Hg are increasingly anesthetic: anesthesia equivalent to 1.0 MAC of halothane in $O_2$ is produced by a $Pa_{CO_2}$ of approximately 245 mm Hg in dogs.[28] Additional studies are necessary to determine the confounding impact of extremes of hypercapnia on anesthetic requirements of horses administered MOR.

The decrease in $Pa_{O_2}$ accompanying the high dose of MOR appeared to be largely related to hypoventilation imposed by MOR. The change in ventilation was largely related to a decrease in alveolar ventilation, because a major change in f was not found in the study (Table 2). The $Pa_{O_2}$ did not vary over time after injection of saline solution. Changes in $Pa_{O_2}$ following injection of the low dose of MOR were similar to those after injection of the high dose of MOR.

Plasma MOR concentration was plotted against time following injection of low and high doses of MOR to horses (Fig 6). Major pharmacokinetic variables describing the disposition of MOR were calculated (Table 4). Comparable data for anesthetized horses are unavailable. The plasma half-life reported in another study[29] in which investigators administered 0.1 mg of MOR/kg, IV, in awake horses was 87.9 minutes. In that study, MOR concentrations in extracted plasma samples were quantified by use of gas chromatography of a pentafluoropropionic anhydride derivative. Half-life of MOR in that study was shorter than previously reported and appears to be dose related on the basis of results from the study reported here. The apparent volume of distribution, which indicates the extent of distribution of the drug, was larger but not significantly different for the high dose of MOR. Because systemic clearance of MOR was not influenced by the dose administered, slower overall elimination could be attributed to wider extravascular distribution at the higher dose. The apparent volume of the central compartment of the 2-compartment model was not significantly different for the 2 doses of MOR.

Values of the major pharmacokinetic variables for MOR in horses differ only slightly from those in dogs, monkeys, and pigs.[5] This supports the view that disposition kinetics of the drug do not account for the variation, especially in CNS (behavioral) effect that is prominent among these species.

Duration of anesthesia after injection of the high dose of MOR was significantly longer than the duration after injection of saline solution or the low dose of MOR. Duration of the experiments was purposely increased after injection of the high dose of MOR to permit prolonged testing of MAC and thereby ensure our ability to observe return of MAC to baseline values. In our experience, horses recovering from equally long or longer periods of ISO (and other forms of) inhalation anesthesia in controlled laboratory experi-

ments do not commonly display the behavior observed in the study reported here for the high-dose of MOR. Because of the results of this study and our knowledge of opioid action in awake and otherwise unmedicated horses,[10,11,30,31] we associated the more undesirable recovery behavior described here with residual CNS-stimulating locomotor effects of MOR, as opposed to simply effects of prolonged general anesthesia and recumbency.

In these experiments, naloxone (0.005 mg/kg, IV) was administered to 2 horses a few moments before cessation of ISO administration. Ventilation improved and $Paco_2$ decreased, presumably as a result of partial antagonism of opioid action in the CNS. However, behavior of these 2 horses during recovery from anesthesia was within the undesirable range of responses and similar to the other 4 horses that did not receive naloxone. In 1 study,[30] it was reported that locomotor stimulation produced by MOR (2.4 mg/kg, IV) in awake horses was reduced by 75% after IV administration of naloxone (0.02 mg/kg). At least part of the difference in results between that study and the study reported here relates to the substantial difference in naloxone dose. Although the number of observations in the study reported here is too small to enable us to make far-reaching conclusions, analysis of our results suggests that on a dose-response spectrum scale, behavioral effects of MOR occur earlier than its respiratory (and perhaps analgesic) effects.

Behavioral characteristics for a horse recovering from general anesthesia after administration of the high dose of MOR were clearly not desirable. Such actions are a substantial threat to the well-being of the horse and to people and property in close proximity. The fact that similar behavior was not seen after injection of the low dose of MOR does not necessarily imply that such a dose of MOR would not adversely impact recovery behavior in other conditions, such as shorter duration of anesthesia associated with rapidly completed surgeries. Presumably, behavioral actions are linked, at least in part, to plasma MOR concentration. Most anesthetic episodes in private clinical practice are of a substantially shorter duration than that used in the study reported here, implying that plasma MOR concentrations would be greater in those situations (Fig 6), perhaps within the range that would result in adverse recovery behavior and associated complications.

In the study reported here, we characterized pharmacokinetic and pharmacodynamic effects of 2 doses of MOR in ISO-anesthetized horses. Qualitatively and quantitatively, MOR had an inconsistent influence on the anesthetic requirement (ie, MAC) for ISO (primarily no change in MAC, but an increase or a small decrease in MAC in some horses). Injection of the high dose of MOR depressed ventilation (ie, increased $Paco_2$). Undesirable and dangerous behavior during recovery from anesthesia accompanied use of the high dose of MOR, which was still evident even after 4 hours of anesthesia maintained by administration of ISO. Results of this study do not support routine clinical use of MOR at the doses used as an adjuvant for ISO in anesthetic management of horses.

[a]Model 7P80 3ECG amplifier, Grass Instruments, Quincy, Mass.
[b]2100 Tele-thermometer, Yellow Springs Instrument Co, Yellow Springs, Ohio.
[c]LB-2 anesthetic analyzer, Sensormedics Corp, Anaheim, Calif.
[d]Primary gas standards, Matheson Gas Products, Newark, Calif.
[e]OM-11, Sensormedics Corp, Anaheim, Calif.
[f]LB-2 $CO_2$ analyzer, Sensormedics Corp, Anaheim, Calif.
[g]ABL 330, Radiometer America, Cleveland, Ohio.
[h]Pharmacokinetic software, Scientific Consulting Inc, Apex, NC.
[i]Sigma Stat 2.03, SPSS Inc, Chicago, Ill.

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