Influence of morphine sulfate on the halothane sparing effect of xylazine hydrochloride in horses

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Objective—To quantitate the dose and time-related effects of morphine sulfate on the anesthetic sparing effect of xylazine hydrochloride in halothane-anesthetized horses and determine the associated plasma xylazine and morphine concentration-time profiles.

Animals—6 healthy adult horses.

Procedure—Horses were anesthetized 3 times to determine the minimum alveolar concentration (MAC) of halothane in O₂ and characterize the anesthetic sparing effect (ie, decrease in MAC of halothane) by xylazine (0.5 mg/kg, IV) administration followed immediately by IV administration of saline (0.9% NaCl) solution, low-dose morphine (0.1 mg/kg), or high-dose morphine (0.2 mg/kg). Selected parameters of cardiopulmonary function were also determined over time to verify consistency of conditions.

Results—Mean (±SEM) MAC of halothane was 1.05 ± 0.02% and was decreased by 20.1 ± 6.6% at 49 ± 2 minutes following xylazine administration. The amount of MAC reduction in response to xylazine was time dependent. Addition of morphine to xylazine administration did not contribute further to the xylazine-induced decrease in MAC (reductions of 21.9 ± 12.0 and 20.7 ± 15.5% at 43 ± 4 and 40 ± 4 minutes following xylazine-morphine treatments for low- and high-dose morphine, respectively). Overall, cardiovascular and respiratory values varied little among treatments. Kinetic parameters describing plasma concentration-time curves for xylazine were not altered by the concurrent administration of morphine.

Conclusions and Clinical Relevance—Administration of xylazine decreases the anesthetic requirement for halothane in horses. Concurrent morphine administration to anesthetized horses does not alter the anesthetic sparing effect of xylazine or its plasma concentration-time profile. (Am J Vet Res 2004; 65:519–526)

α₂-Adrenergic receptor agonists cause sedation and analgesia and as a result are commonly administered to horses as adjuvants for inhalation anesthesia. α₂-Adrenergic receptor agonists were the first class of agents that were shown to significantly and consistently reduce inhalation anesthetic requirements (ie, median effective dose or minimum alveolar concentration [MAC] of an inhalation anesthetic) in horses. These results are in contrast to the notably inconsistent effects of at least some opioid drugs when used alone as an inhalation anesthetic adjuvant in horses. Nevertheless, in contemporary clinical practice, it is not uncommon to include an α₂-adrenergic receptor agonist and an opioid drug in the inhalation anesthetic management of horses, despite the absence of clear objective data to support this as routine practice. Accordingly, the objectives of the study reported here were to identify the magnitude and duration of the effect of morphine sulfate on the anesthetic sparing effect of xylazine hydrochloride in halothane-anesthetized horses and determine the concurrent time-related arterial blood concentrations of xylazine and morphine.

Materials and Methods

Horses—Six healthy, unmedicated horses of various breeds (Thoroughbred, Quarter Horse, and Arabian) were studied. They included 5 mares and 1 gelding, which were (mean ± SE) 4.0 ± 0.5 years old and weighed 484 ± 18 kg. The Animal Use and Care Administrative Advisory Committee of the University of California at Davis approved the study protocol.

All horses were anesthetized on 3 occasions, at least 2 weeks apart. In every horse, the MAC of halothane was first determined (in triplicate) prior to administration of any other agent. Horses then received 1 of 3 randomly assigned drug combinations IV, and the MAC of halothane was re-determined multiple times during the remaining period of general anesthesia. Feed was withheld for 12 hours before induction of anesthesia, but water was always available.

Study conditions—Anesthesia was induced in nonmedicated horses by use of only halothane in O₂ as previously

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The inhaled anesthetic was delivered to horses via a mask connected to a large animal anesthetic circuit system. Orotracheal intubation by use of a 30-mm-internal-diameter, cuffed endotracheal tube was performed when anesthetic depth was suitable (ie, at 10 to 15 minutes). Following intubation, horses were positioned in left lateral recumbency on a thick foam-padded cart and transported to the laboratory without being disconnected from the breathing circuit. After arriving in the laboratory, horses were prepared for study during the remainder of the first hour of anesthesia. A calibrated thermistor probe was positioned in the nasopharynx to measure body temperature. Body temperature was maintained constant either by use of heat lamps if it decreased or fans and ice if it started to increase. A base-apex lead ECG was used to monitor heart rate and rhythm. An 18-gauge, 5.08-cm-long catheter was inserted percutaneously into the right facial artery for direct measurement of systemic arterial blood pressure. The catheter was connected to a strain gauge position level with the sternum. The strain gauge was calibrated at the beginning of each experimental day by use of a mercury column. The arterial catheter was also used for collection of blood samples for determination of plasma drug concentrations and for measurement of blood gas tensions (ie, PaO2, PaCO2) and pH. 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 aseptically catheterized within 30 to 45 minutes following the first breath of halothane (ie, start of anesthetic induction) to allow for continuous urine drainage throughout anesthesia and minimal urinary bladder size during anesthetic recovery.

End-expired gas samples were obtained by intermittent hand sample collection from a nylon catheter positioned near the caudal tip of the tracheal tube. Halothane was measured with an infrared gas absorption technique with calibration by use of at least 7 tank standards before the start of each study. Calibration checks were also made throughout the study day. Final halothane values were corrected according to the calibration curves obtained at the beginning of each experimental day by use of at least 7 tank standards before the start of each study. The arterial catheter was used for collection of blood samples for determination of plasma drug concentrations and for measurement of blood gas tensions (ie, PaO2, PaCO2) and pH. Blood gas tensions were also collected into plain glass tubes before and at 5, 10, 15, 30, 60, 90, 120, 150, and 180 minutes after xylazine administration, for measurement of PaO2, PaCO2, and pH. Measurements were made within a few minutes of sample collection. Results were corrected on the basis of the horse’s pharyngeal temperature.

Cardiopulmonary measurements—Carotid arterial blood pressure and heart rate were determined from recordings made 30 to 60 seconds before noxious stimulation. To minimize differences caused by the effect of differing halothane concentrations, cardiopulmonary values obtained at paired time points used to also characterize MAC were averaged, and the means were considered the heart rate and blood pressure values at MAC. Values for respiratory frequency were obtained in a similar manner.

Blood gas tension measurements—Arterial blood samples were collected in heparinized syringes periodically before xylazine was administered, which was at or near the MAC of halothane and at 60, 90, 120, 150, and 180 minutes after xylazine administration, for measurement of PaO2, PaCO2, and pH. Measurements were made within a few minutes of sample collection. Results were corrected on the basis of the MAC returned to within at least 10% of the predrug MAC measurement or to about 200 minutes following xylazine administration.

Plasma drug measurements—Arterial blood samples were also collected into plain glass tubes before and at 5, 10, 15, 30, 60, 90, 120, 150, and 180 minutes after drug administration for later determination of plasma xylazine and morphine concentrations. The blood was allowed to clot after which the tubes were placed in a centrifuge, and the serum was collected and stored frozen at –70°C until analyzed.

Analytical procedure for determination of plasma xylazine concentrations—Analytical grade xylazine was dissolved in methanol to produce a standard solution of 10 mg/mL. Plasma calibrators were prepared by adding the appropriate volumes of the drug to drug-free equine plasma to produce plasma xylazine concentrations of 2, 10, 200, 300, 500, 700, 1,000, and 2,000 ng/mL. Quality control samples were prepared in a similar manner in drug-free equine plasma at concentrations of 40, 200, and 800 ng/mL.
Calibrators and quality control samples were prepared fresh on the day of analysis. Two negative controls were also prepared for each set of calibrators.

For the analysis, the samples (ie, calibrator, quality control, and unknown samples) were vortexed for 5 to 10 seconds after which 0.5 mL of each was pipetted into a 1.5 mL microcentrifuge tube. Then 0.6 mL of a 9 parts acetonitrile (ACN; high-performance liquid chromatography grade) to 1 part 1 M acetic acid solution was added to each tube, and the tubes were vortexed for 1 minute and then refrigerated for 1 hour. After refrigeration, the tubes were centrifuged in a microcentrifuge at 3,000 x g for 4 minutes and the supernatant solutions transferred to autosampler vials. Analysis was performed by use of gas chromatography-mass spectrometry with quantifying ions of 221 and 90. Solvents included ACN with 0.1% trifluoroacetic acid (TFA) and water with 0.1% TFA. Solvent flow rate was 0.5 mL/min. The solvent gradient was set up as follows: 1 minute, 10% ACN with 0.1% TFA; 5.5 minutes, 80% ACN with 0.1% TFA; 6 minutes, 90% ACN with 0.1% TFA; and 6.01 minutes, 10% ACN with 0.1% TFA.

The slope, intercept, and correlation coefficient for each calibration curve were calculated by linear regression analysis of the concentration of xylazine in unknown samples was calculated from the slope and intercept of the calibration curve.

Analytical procedure for determination of plasma total morphine concentrations—A standard solution of morphine sulphate in methanol was purchased at a morphine base concentration of 1 mg/mL. A standard solution of an isotopically labeled form of morphine containing 3 deuterium atoms/molecule (ie, deuterium-labeled morphine) was purchased in methanol at a concentration of 0.1 g/L. The standard solution of morphine was serially diluted with methanol to produce working solutions at morphine concentrations of 10 and 1 ng/mL. The standard solution of deuterium-labeled morphine was diluted with methanol to produce a working solution concentration of 10 ng/mL. Plasma calibrators were prepared by adding the appropriate volumes of the working standard solutions of morphine to 13 x 100-mm screw cap tubes; the methanol was evaporated under nitrogen, and drug-free equine plasma was added to produce morphine plasma concentrations of 5, 10, 30, 50, 100, 150, and 200 ng/mL. Quality control samples were prepared in a similar manner in plasma at concentrations of 5, 40, and 200 ng/mL. Calibrators and quality control samples were prepared fresh on the day of analysis. Two negative controls were also prepared for each set of calibrates. For those unknown samples determined to have morphine concentrations > 200 ng/mL, the samples were diluted with drug-free equine plasma and 0.5 mL of the diluted sample was retested.

For the analysis, 50 ng of deuterium-labeled morphine was added to vials containing 0.5 mL of plasma (calibrator, quality control, and unknown samples). Samples were made alkaline with 1 mL of 1 M carbonate buffer (pH 9), and after brief vortex-mixing, 2 mL of n-butyl chloride-methylene chloride (3:1, vol/vol) was added to each tube. The samples were mixed, and the aqueous layer was frozen in a dry ice-acetone bath. The organic phase was decanted and evaporated at 40°C to 50°C under a stream of nitrogen.

The dry residues were derivatized by the addition of 50 µL of pentafluoropropionic acid and 50 µL of ACN. The samples were incubated at 70°C for 1 hour, then cooled to room temperature (approx 20°C to 22°C), centrifuged (1,056 x g) for 2 minutes, and evaporated to dryness under a stream of nitrogen at 40°C to 50°C for 45 minutes. The samples were then dissolved in 50 µL of toluene, briefly vortex-mixed, and then sonicated and centrifuged (1,056 x g) for 1 minute. The samples were transferred to 300-µL autosampler vials, and 1 µL was injected into the gas chromatography-mass spectrometer by use of a splitless mode.

Analyses were performed on a mass spectrometer interfaced to a gas chromatograph with electronic flow control. The mass spectrometer was operated in El mode (energy of 70 eV) by use of high purity helium maintained at a constant flow rate of 1 mL/min as the carrier gas. The detector was operated in selected-ion monitoring mode by use of m/z 414.4 and m/z 417.4 to detect the morphine and deuterium-labeled morphine (internal standard) derivatives, respectively. The dwell time for each ion was 25 milliseconds.

The ratios of the areas of the morphine derivative ion (m/z 414.4) and the deuterium-labeled morphine ion (m/z 417.4) were calculated and plotted against the known concentration of morphine in plasma calibrators. The slope, intercept, and correlation coefficient for each calibration curve was calculated by linear regression analysis. The concentration of morphine in unknown samples was calculated from the slope and intercept of the calibration curve. For those unknown samples with a morphine concentration of < 50 ng/mL, the calibration curve consisted of the calibrators from 5 through 50 ng/mL. For those samples with a morphine concentration ≥ 50 ng/mL and ≤ 200 ng/mL, the calibration curve consisted of the calibrators from 5 through 200 ng/mL.

Statistical analysis—Values are expressed as means (± SEM), unless indicated differently. Inferential statistics include 1-way and 2-way repeated measures ANOVA and associated posthoc Bonferroni (multiple comparisons vs control) and Tukey (used for multiple pairwise comparisons) tests. The raw and logarithmically transformed data were used as appropriate in the analyses. The peri-anesthetic, predrug data were considered baseline for the blood gas tension data analysis. A value of P < 0.05 was considered significant.

The plasma xylazine and morphine concentration-time data were analyzed by nonlinear least squares regression analysis with equal weighting of the data by use of commercial software. The pharmacokinetic terms describing the disposition of both xylazine and morphine were calculated from the dose administered and the experimentally derived constants describing the equation of the curve that best fit the plasma concentration-time profile for each horse. As with other data, the individual horse data were then grouped and summarized as mean ± SEM. The calculated parameters were the elimination half-life, the area under the concentration versus time curve, the volume of distribution at steady state, the volume of the central compartment, and the systemic clearance.

Results

No difference was found in anesthetic duration in horses between saline treatment and xylazine-mor-
phine treatments was 20.9 ± 2.2%. The decrease occurred 44.1 ± 2.5 minutes after xylazine administration, and no treatment effect (ie, morphine or saline solution) was observed (Table 1). Minimum alveolar concentration data from individual horses were grouped according to treatment and time and summarized. The MAC of halothane obtained following xylazine-saline treatment was determined. Graphic summaries of the rate of return of MAC values toward predrug MAC values following xylazine-saline treatment were produced (Fig 2 and 3). Changes in the MAC of halothane following xylazine administration in the study reported here were compared with changes in the MAC of isoflurane following administration of the same dose of xylazine in another study1 and were found to be similar.

A graphic comparison of the return in MAC values to predrug MAC values following xylazine-morphine treatments was produced (Fig 3). Neither xylazine-morphine treatment (ie, low- or high-dose morphine) resulted in an MAC decrease that was different from that following xylazine-saline treatment; a faster rate of return to the predrug MAC value was found following xylazine-morphine treatments, especially following administration of high-dose morphine, but this finding was not significant.

Cardiopulmonary responses—Three measurements of heart rate, mean arterial pressure, and respiratory rate were obtained at approximately the same time during anesthesia for each treatment and summarized. One set of measurements was obtained before treatment, and 2 sets of measurements were obtained following xylazine-saline and xylazine-morphine treatments (Table 2). These results have not been subject to inferential analyses. Our intent was to provide limited summarized data at similar time points during anesthesia to indicate that typical physiologic conditions in horses anesthetized with inhalation agents prevailed. We reasoned inferential analyses were therefore unnecessary.

Table 1—Mean (± SEM) minimum alveolar concentration (MAC) of halothane in 6 horses before and after IV administration of xylazine hydrochloride (0.5 mg/kg, IV) followed immediately by IV administration of saline (0.9% NaCl solution) or morphine sulfate

<table>
<thead>
<tr>
<th>Morphine dose</th>
<th>MAC</th>
<th>Pharyngeal temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>1.07 ± 0.05</td>
<td>37.8 ± 0.1</td>
</tr>
<tr>
<td>0.1 mg/kg</td>
<td>1.01 ± 0.03</td>
<td>38.0 ± 0.2</td>
</tr>
<tr>
<td>0.2 mg/kg</td>
<td>1.06 ± 0.02</td>
<td>38.2 ± 0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Change in MAC (%)</th>
<th>Pharyngeal temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 ± 2</td>
<td>0.379 ± 0.1</td>
<td>37.9 ± 0.1</td>
</tr>
<tr>
<td>43 ± 4</td>
<td>0.379 ± 0.1</td>
<td>38.1 ± 0.2</td>
</tr>
<tr>
<td>40 ± 4</td>
<td>0.379 ± 0.1</td>
<td>38.3 ± 0.2</td>
</tr>
</tbody>
</table>
Changes in arterial blood base balance following xylazine-morphine administration. For brevity, summarized pHa and base balance data are not included. During anesthesia each horse also received saline solution (IV), low-dose morphine (0.1 mg/kg), and high-dose morphine (0.2 mg/kg). Anesthetic depth is equipotent with each horse and condition.

**Blood gas tension analysis**—Arterial blood gas tension values before and after xylazine-saline and xylazine-morphine treatments were summarized (Table 3). The values for PaO₂ and PaCO₂ immediately before xylazine administration (ie, control values) did not differ among treatments. No significant difference in the mean values of PaO₂ and PaCO₂ was found between low- or high-dose morphine administration (time factor) and either saline solution or morphine in 6 horses anesthetized with halothane.

**Pharmacokinetics of xylazine and morphine**—Following xylazine-saline and xylazine-morphine treatments, the decline in plasma concentrations of xylazine over time (Fig 4) was best described in at least 5 out of 6 horses by a biexponential equation as follows:

\[ C_p = A e^{-\alpha t} + B e^{-\beta t} \]

where \( C_p \) is the concentration of xylazine in plasma at time \( t \), \( A \) and \( B \) are the y-axis intercepts of the extrapolated plasma drug concentrations decay curves, and \( \alpha \) and \( \beta \) are the hybrid rate constants related to slopes of the distribution and elimination phases, respectively. Kinetic parameters describing the plasma concentration-time curve for xylazine were not significantly altered by the concurrent administration of morphine at a dose of 0.1 or 0.2 mg/kg (Table 4).

Following both xylazine-morphine treatments, the decline in plasma concentrations of morphine over time (Fig 5) was best described in all horses by a triexponential equation as follows:

\[ C_p = P e^{-\alpha t} + A e^{-\beta t} + B e^{-\gamma t} \]
The MAC of halothane required to maintain constant time was plotted along with the time-related change in concentration-time curve. No significant differences were found between the 2 doses of morphine in the remaining kinetic parameters describing the plasma concentration-time curve.

The decay of plasma xylazine concentration with time was plotted along with the time related change in the MAC of halothane required to maintain constant anesthetic conditions (Fig 6). From these time-related relationships we estimated that the mean decreases in the MAC of halothane of 18.5% and 13.3% were related to slopes of the rapid and slow distribution and elimination phases, respectively.

### Table 4—Mean (± SEM) pharmacokinetics values for xylazine in 6 halothane-anesthetized horses after receiving a single IV dose of xylazine (0.5 mg/kg) followed immediately by either saline solution (0.9% NaCl) or morphine administration

<table>
<thead>
<tr>
<th>Kinetic parameters</th>
<th>Saline (n = 6)</th>
<th>0.1 (6)</th>
<th>0.2 (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀ (µg/mL)</td>
<td>3.75 ± 1.00</td>
<td>1.92 ± 0.19</td>
<td>2.07 ± 0.18</td>
</tr>
<tr>
<td>A (µg/mL)</td>
<td>2.44 ± 0.05</td>
<td>1.42 ± 0.15</td>
<td>1.63 ± 0.28</td>
</tr>
<tr>
<td>B (µg/mL)</td>
<td>0.44 ± 0.07</td>
<td>0.49 ± 0.05</td>
<td>0.47 ± 0.08</td>
</tr>
<tr>
<td>α (min⁻¹)</td>
<td>0.23 ± 0.04</td>
<td>0.18 ± 0.02</td>
<td>0.17 ± 0.12</td>
</tr>
<tr>
<td>β (min⁻¹)</td>
<td>0.006 ± 0.001</td>
<td>0.006 ± 0.001</td>
<td>0.004 ± 0.001</td>
</tr>
<tr>
<td>t_{1/2}(min)</td>
<td>117.8 ± 19.7</td>
<td>143.7 ± 25.3</td>
<td>157.5 ± 18.9</td>
</tr>
<tr>
<td>AUC (µg/min/mL)</td>
<td>113.6 ± 25.2</td>
<td>107.9 ± 20.6</td>
<td>112.2 ± 21.8</td>
</tr>
<tr>
<td>V₁ (mL/kg)</td>
<td>5.7 ± 1.1</td>
<td>5.8 ± 1.1</td>
<td>5.0 ± 0.7</td>
</tr>
<tr>
<td>V_{dissolv}(mL/kg)</td>
<td>757 ± 120</td>
<td>879 ± 83</td>
<td>967 ± 169</td>
</tr>
<tr>
<td>V₃ (mL/kg)</td>
<td>180 ± 36</td>
<td>277 ± 34</td>
<td>242 ± 20</td>
</tr>
</tbody>
</table>

No significant differences were found related to treatment for any parameter. 

C₀ = Concentration of xylazine in plasma at time 0. A and B = Y-intercepts of the extrapolated plasma drug concentrations decay curves. α and β = Hybrid rate constants related to slopes of the distribution and elimination phases, respectively. t_{1/2} = Elimination half-life. AUC = Area under the concentration versus time curve; Clₚ = Systemic clearance. V_{dissolv} = Total volume of distribution. V₃ = Volume of the central compartment.

### Table 5—Mean (± SEM) pharmacokinetics values for morphine in 6 halothane-anesthetized horses after receiving a single IV dose of xylazine (0.5 mg/kg) followed immediately by morphine administration

<table>
<thead>
<tr>
<th>Kinetic parameters</th>
<th>Morphine (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 (n = 6)</td>
</tr>
<tr>
<td>C₀ (µg/mL)</td>
<td>3.21 ± 0.53</td>
</tr>
<tr>
<td>P (µg/mL)</td>
<td>3.00 ± 0.52</td>
</tr>
<tr>
<td>A (µg/mL)</td>
<td>0.06 ± 0.016*</td>
</tr>
<tr>
<td>B (µg/mL)</td>
<td>0.014 ± 0.001*</td>
</tr>
<tr>
<td>α (min⁻¹)</td>
<td>0.53 ± 0.03</td>
</tr>
<tr>
<td>β (min⁻¹)</td>
<td>0.11 ± 0.01</td>
</tr>
<tr>
<td>t_{1/2}(min)</td>
<td>95.4 ± 11.2</td>
</tr>
<tr>
<td>AUC (µg/min/mL)</td>
<td>8.32 ± 0.87*</td>
</tr>
<tr>
<td>V₁ (mL/kg)</td>
<td>1795 ± 379</td>
</tr>
<tr>
<td>V₃ (mL/kg)</td>
<td>37.67 ± 6.71</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) differences between low- or high-dose morphine administration. P, A, and B = Y-axis intercepts of the extrapolated plasma drug concentrations decay curves. P, α, and β = Hybrid rate constants related to slopes of the rapid and slow distribution and elimination phases, respectively.

See Table 4 for remainder of key.

Figure 5—Mean (± SEM) plasma morphine concentration versus time in 6 halothane-anesthetized horses following IV administration of xylazine (0.5 mg/kg, IV) and low-dose morphine (0.1 mg/kg) or high-dose morphine (0.2 mg/kg). Anesthetic depth is equipotent with each horse and condition.

Figure 6—Mean (± SEM) percent change in MAC of halothane and plasma xylazine concentration versus time in 6 horses. Zero time represents the time of xylazine administration (0.5 mg/kg, IV bolus) in halothane-anesthetized horses. Following xylazine administration, the alveolar halothane concentration was periodically adjusted to maintain the depth of anesthesia (via halothane and xylazine) relatively constant and equivalent to a multiple of 1.0 MAC for halothane alone.

### Discussion

In our study, the MAC of halothane determined prior to the administration of xylazine, with or without morphine, in each horse was similar (Table 1) and the overall mean MAC of halothane (ie, 1.05 ± 0.02%) was consistent with results of other studies on halothane requirements in horses from this laboratory (MAC range of 0.88% to 1.05%10). In a study on horses, xylazine administration caused a consistent decrease in the MAC of isoflurane.1 The magnitude of the effect of xylazine on the MAC of isoflurane was dose and time
related. We compared our results visually with those of the previous study (Fig 2). The decrease in MAC by xylazine administration alone and the time of diminishing effect after xylazine administration is similar in halothane- and isoflurane-anesthetized horses. The lack of a difference in terms of inhalation anesthetic was not surprising on the basis of earlier work with dogs. Our results confirm previous findings of a consistent and substantial anesthetic sparing effect of xylazine in horses. These data are evidence that xylazine administration provides a benefit when used as an adjunct to inhalation anesthesia.

The consistent and similar decrease in the MAC of halothane caused by xylazine administration was not significantly altered by either dose of morphine administered in our study. In a recent study on morphine action in isoflurane-anesthetized horses, the influence on MAC by morphine (0.25 mg/kg, IV) administration was inconsistent. In the 6 horses of that study, 3 had an increase in the MAC of isoflurane in response to morphine administration. 1 had a decrease in MAC, and 2 did not have a change in MAC. Methods used in that study did not differ from those of our study except that isoflurane was the inhalation anesthetic agent, as opposed to halothane, and xylazine was not administered. Perhaps it is not surprising that no additional change in MAC has been detected with the addition of morphine to xylazine administration. The doses of morphine used in our study were based on those commonly used and on data from another study. In that study, the morphine dose was 0.05 mg/kg greater than the largest dose used in our study and the maximal change in MAC following morphine (0.25 mg/kg) administration ranged only from −20.2% to +28.3%. Given the small time-related peak effect, the morphine dose differences (even though slight) between the 2 studies, and the addition of xylazine, it is possible that any changes in MAC accorded to morphine could not be detected above experimental “noise.” Another interesting comparison is that the time-related plasma morphine concentrations in horses are considerably lower than those similarly obtained from, and known to be effective in, dogs and nonhuman primates (nearly an order of magnitude different). Regardless, in our study the addition of morphine did not contribute to a decrease in anesthetic requirement by xylazine administration. Consequently, these results do not support widespread indiscriminate use of morphine (at least at the doses studied) to improve general anesthetic conditions for horses.

Predrug conditions were typical of horses anesthetized with a low dose (ie, multiple of 1.0 MAC) of halothane in O2. Circumstances following xylazine administration seem qualitatively similar to results previously published for xylazine actions in isoflurane-anesthetized horses. On the other hand, morphine seemed to influence heart rate and mean arterial pressure less in our study than previously observed. Presumably any influence of morphine was largely counterbalanced by the actions of xylazine in our study rather than an effect imposed by background halothane versus isoflurane anesthesia. Blood gas tension values in halothane-anesthetized horses in our study before administration of adjuvant drugs were similar to reported values for like conditions. The PaCO2 did not change significantly with time following either xylazine and saline solution administration or xylazine and low-dose morphine administration, but high-dose morphine administration was associated with a significant increase. This change was presumably related to the added actions of morphine; although it is interesting that in our previous study on isoflurane-anesthetized horses, a similar dose of only morphine did not cause a significant change in PaCO2. Although the cause for this difference is not clear, notable differences in PaCO2 response may be related to differences in inhalation agents or an additive effect of xylazine administration with morphine. Alternatively, this observation may just be a chance-related result. Regardless, until further work clarifies the influence of opioid with or without an accompanying α2-adrenergic receptor agonist drug on the magnitude of PaCO2 in anesthetized horses, caution in their use under similar conditions is warranted.

Plasma concentrations of morphine during general anesthesia have been reported for horses, but to our knowledge, this is the first such report of xylazine data. Our data contribute to an advancement of knowledge in a number of ways. First, with some allowance for differences in techniques, the results derived from our study compare favorably with, and therefore confirm that of, studies of awake and anesthetized equids with similar doses of either xylazine or morphine when given alone. If the mild alteration in plasma kinetics of xylazine is not merely a chance occurrence, it can be easily further explained by the influence of associated conditions of general anesthesia. Conditions of general anesthesia would be expected to decrease total body drug clearance and apparent volume of distribution and increase plasma morphine half-life. Our data suggest that morphine when given in conjunction with xylazine in anesthetized horses does not alter the plasma kinetics of xylazine (Fig 4). On the other hand, a comparison of our data with that of a recent similar study on morphine administration alone suggests that the accompanying xylazine in our study may have decreased the plasma clearance of morphine and increased its plasma half-life. This indirect finding supports results and speculation from a previous study on alfentanil administration in halothane-anesthetized horses, but it seemingly conflicts with an increased clearance that might be predicted in association with the well known increased urinary output commonly associated with halothane. Third, data from our study provides kinetic information that may be used to facilitate more precise dosing of both xylazine and morphine in clinical situations by use of continuous rate-infusion methods to manage general anesthesia in horses. Finally, characterizing the plasma drug concentration-time profile of xylazine in conjunction with our estimate of its halothane anesthetic sparing effect (Fig 6) permits at least a crude correlation between
the plasma concentration of xylazine and the intensity of its sedative and analgesic actions in horses.

References