Effects of high plasma fentanyl concentrations on minimum alveolar concentration of isoflurane in horses

Heather K. DiMaio Knych, DVM, PhD; Eugene P. Steffey, VMD, PhD; Khursheed R. Mama, DVM; Scott D. Stanley, PhD

Objective—To verify the isoflurane anesthetic minimum alveolar concentration (MAC)-sparing effect of a previously administered target plasma fentanyl concentration of 16 ng/mL and characterize an anticipated further sparing in isoflurane MAC associated with higher target plasma fentanyl concentrations.

Animals—8 horses.

Procedures—Horses were assigned 2 of 3 target plasma fentanyl concentrations (16, 24, and 32 ng/mL), administered in ascending order. Following determination of baseline MAC, horses received a loading dose of fentanyl followed by a constant rate infusion; MAC determination was performed in triplicate at baseline and at each fentanyl concentration. Venous blood samples were collected throughout the study for determination of actual plasma fentanyl concentrations. Recovery from anesthesia was monitored, and behaviors were rated as excellent, good, fair, or poor.

Results—Mean ± SD fentanyl plasma concentrations were 13.9 ± 2.6 ng/mL, 20.1 ± 3.6 ng/mL, and 24.1 ± 2.4 ng/mL for target concentrations of 16, 24, and 32 ng/mL, respectively. The corresponding changes in the MAC of isoflurane were –3.28%, –6.23%, and +1.14%. None of the changes were significant. Recovery behavior was variable and included highly undesirable, potentially injurious excitatory behavior.

Conclusions and Clinical Relevance—Results of the study did not verify an isoflurane-sparing effect of fentanyl at a plasma target concentration of 16 ng/mL. Furthermore, a reduction in MAC was not detected at higher fentanyl concentrations. Overall, results did not support the routine use of fentanyl as an anesthetic adjuvant in adult horses. (*Am J Vet Res* 2009;70:1193–1200)

Opioid drugs are commonly administered to patients to relieve moderate and severe pain. Because of their potent analgesic properties, opioids are commonly coadministered with inhalation anesthetic agents to reduce the concentration of the inhaled agent necessary for anesthesia, and as a result they decrease anesthesia-related cardiovascular depression. Fentanyl is a potent, short-acting member of the opioid drug class, and its ability to reduce inhalation anesthetic requirement, as defined by the MAC, in a variety of species is well known.[1–3] Thus, use of fentanyl for clinical anesthetic management of these species is common.

It is also broadly accepted that morbidity and mortality rates associated with general anesthesia are much greater in horses,[4] compared with the other spe-

Abbreviations

ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
Cl	Clearance
CK	Creatine kinase
CRI	Constant rate infusion
C_T	Target concentration
DAP	Diastolic arterial pressure
HR	Heart rate
IPPV	Intermittent positive pressure ventilation
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
PMA	N-(1-phenyl-4-piperidyl) malonanilinic acid
SAP	Systolic arterial pressure
SDH	Sorbital dehydrogenase
TP	Total protein
V_{dss}	Volume of distribution at steady state

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From the K. L. Maddy Equine Analytical Chemistry Laboratory, California Animal Health and Food Safety Laboratory, and the Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Knych, Steffey, Stanley); and the Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523 (Mama).
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Address correspondence to Dr. Knych (hkknych@ucdavis.edu).

cies commonly anesthetized under clinical conditions. Similar to other species, inhalation anesthetics are commonly administered to equine patients, and depression of cardiovascular function accompanies their use.[5] Accordingly, it is logical to consider coadministration of opioids with inhalation anesthetics for management of horses with the goal of improving anesthetic outcome. However, objective evidence supporting such clinical practice in horses is limited. For example, Steffey et al[6] determined that IV administration of 2 mg of morphine/kg caused a 50% reduction in isoflurane MAC in dogs, but under similar laboratory conditions, the same dose of morphine, at a similar time after administration, caused a much smaller reduction in isoflurane MAC in some horses, an increase in others, and no change in still others.[7] Similarly, alfentanil reduced the MAC of isoflurane in human patients[8] and cats[9] but did not change MAC in horses.[10] However, most recently, Thomasy et al[11] reported a small (18%) decrease in isoflurane MAC when fentanyl was administered, supporting further investigation of opioid use as an adjunct to inhalation anesthesia in equine patients.

In 1 study,[11] 3 targeted plasma concentrations of fentanyl (1, 8, and 16 ng/mL) were studied in 8 horses during anesthesia with only isoflurane in O_2 (no other anesthetic or adjuvant drugs were administered). Mean measured plasma concentrations of fentanyl of 0.7 and 8.5 ng/mL did not cause a change in isoflurane MAC in those horses, but at 13.3 ng/mL, isoflurane MAC decreased by a mean of 18%. These results suggest a dose-dependent favorable response to fentanyl coadministered with isoflurane. Accordingly, the study reported here was designed to verify the isoflurane MAC-sparing effect of a target plasma fentanyl concentration of 16 ng/mL and characterize an anticipated further sparing in isoflurane MAC associated with target plasma fentanyl concentrations of 24 and 32 ng/mL.

Materials and Methods

Horses—Eight healthy unmedicated adult horses including 5 Thoroughbreds, 2 Quarter Horses, and 1 Arabian (7 geldings and 1 mare with a mean ± SD weight of 530 ± 31 kg and mean ± SD age of 12 ± 0.8 years) were studied. Before beginning the study, horses were determined to be healthy by results of physical examination, CBC, and serum biochemistry panel that included activities or concentrations of AST, CK, ALP, total bilirubin, SDH, SUN, and creatinine. Blood analyses were performed by the Clinical Pathology Laboratory of the William R. Pritchard Veterinary Medical Teaching Hospital of the University of California-Davis, by use of standard protocols. The study was approved by the Institutional Animal Care and Use Committee of the University of California-Davis and followed closely in design the study reported by Thomasy et al[11] from this laboratory.

Induction and maintenance of anesthesia—Food, but not water, was withheld from horses for 12 hours prior to anesthesia. Just before induction of anesthesia, 14-gauge catheters were percutaneously placed in the left and right external jugular veins. One catheter was used later for administration of fentanyl and isotonic fluids and the other for blood sample collection. Horses did not receive any premedication or injectable anesthetic drugs. Prior to anesthetic induction, venous blood was drawn for a panel of clinical serum biochemical analyses.

Anesthesia was induced with isoflurane in O_2 via a mask in physically restrained horses positioned in left lateral recumbency on a tiltable large animal surgery table. Once a suitable plane of anesthesia was reached, orotracheal intubation was performed, and anesthesia was maintained via a standard large animal circle breathing system attached to the orotracheal tube.[12] While remaining connected to the breathing circuit, horses were repositioned in left lateral recumbency on a thick pad placed on a mobile cart, for transport to the laboratory. During the first hour of anesthesia, horses were instrumented for the study, and stable anesthetic and ventilatory conditions were established.

Instrumentation—End-tidal gas was obtained by use of a gas-tight glass syringe and hand sampling from a catheter placed within the lumen of the endotracheal tube; the catheter was used to obtain a sample from the distal end of the tracheal tube. Isoflurane concentration in the sample was determined via infrared gas analysis.[a] The anesthetic analyzer was calibrated at the start of each experimental day by use of at least 6 certified compressed gas (secondary) standards from 0% to 3.5% isoflurane. Instrument calibration was frequently checked throughout each individual study day. Measured isoflurane concentration was adjusted for reporting by use of each day's gas calibration curve.

The right facial artery was percutaneously catheterized for measurement of systemic arterial blood pressure and for collection of arterial blood for various analyses. Systolic arterial pressure and DAP were measured via the catheter connected to a strain gauge transducer[b] positioned level with the sternum. The transducer was calibrated at multiple pressures from 0 to 200 mm Hg prior to the beginning of each experiment by use of a mercury column. Recorded pressures were adjusted on the basis of the calibration curve if necessary. Mean arterial pressure was recorded as the electronic mean of the arterial pressure wave. Measurement of HR and evaluation of heartbeat rhythm were accomplished via an ECG[c] with a base-apex configuration. Arterial blood samples were collected at least every 30 minutes in heparinized syringes and analyzed[d] within a few minutes of collection for Pa_{O_2}, Pa_{CO_2}, pH, PCV (via microhematocrit), and TP concentration (via refractometer). For reporting, measured blood gas and pH values were mathematically corrected to the horse's nasopharyngeal temperature measured at the time of sampling by use of a calibrated thermister.[e] When necessary, heat lamps or alcohol splashes or ice were used to maintain rectal temperature at 36° to 38°C. Lactated Ringer's solution was administered IV throughout anesthesia at a rate of 2 to 4 mL/kg/h.

To override respiratory depressant effects of isoflurane and perhaps fentanyl, IPPV was applied during anesthesia by use of a locally constructed bag-in-barrel system[f] that replaced the rebreathing bag of the large animal breathing circuit. Peak inspiratory pressure, measured at the proximal end of the endotracheal tube

(ie, circle system Y-piece juncture), was maintained at 18 to 22 cm H_2O (via a water-manometer–calibrated aneroid manometer), and respiratory frequency was adjusted to maintain $Paco_2$ at 40 to 50 mm Hg. A urinary catheter was aseptically positioned with its tip in the urinary bladder and connected to a receptacle to permit continuous urine drainage throughout anesthesia.

Determination of MAC—During the second half of the first hour of anesthesia, horses were maintained at an end-tidal isoflurane concentration of 1.5% to 2.0%. Baseline isoflurane MAC was started at the end of the first hour of anesthesia by use of a protocol reported for this laboratory.[11] Briefly, end-tidal isoflurane concentration was initially adjusted to an arbitrary value of 1.3% to 1.7% and was then maintained constant for at least 20 minutes. At the end of this 20-minute end-tidal isoflurane equilibration period, but prior to noxious stimulation, values for HR, SAP, DAP, MAP, and temperature were recorded. Arterial blood was sampled for blood gas, pH, PCV, and TP analyses. A sample of jugular venous blood was also obtained for later analysis of plasma fentanyl concentration and its primary metabolite, PMA.[13] Immediately following these events, an electrical stimulus (50 V, 5 Hz, 10 milliseconds; considered supramaximal) was applied for up to 1 minute via needle electrodes inserted just under the oral mucous membrane of the rostrolateral aspect of the right maxilla. A positive response to stimulus was judged as gross purposeful movement of the head, neck, 1 or more limbs, or some combination thereof. At the conclusion of each stimulus event, HR and arterial blood pressures were again recorded. Immediately following these measurements, the inspired isoflurane concentration was either increased or decreased according to the just observed response to noxious stimulation. Stepwise changes (up or down) in isoflurane concentration were approximately 10% but not > 20% (relative). Following a paired positive and negative event, the isoflurane MAC was calculated as the calibration-curve corrected isoflurane concentration midway between that allowing and that preventing gross purposeful movement. The recorded isoflurane concentrations at MAC for each of the 3 conditions (ie, baseline representing only isoflurane anesthesia plus 2 conditions of fentanyl administration) studied in each horse represent triplicate determination of MAC at each of the 3 study conditions.

Fentanyl administration—Each horse was randomly assigned to receive only 2 of 3 target plasma fentanyl concentrations (16, 24, and 32 ng/mL). In every instance, the doses assigned were administered IV in ascending order during a single anesthetic episode. Isoflurane MAC was first determined in the absence of fentanyl (baseline) and then at each target fentanyl concentration assigned to the individual studied. To minimize overshooting the target plasma fentanyl concentration and the potential for CNS excitation, fentanyl was initially administered as a loading (ie, bolus) dose over the course of 12 minutes. The loading dose of fentanyl was determined by use of the following equation: loading dose = $C_T \times V_{dss}$. The V_{dss} used (0.26 L/kg) was determined in a pharmacokinetic study of isoflurane-anesthetized horses.[13] Target plasma fentanyl concentrations were maintained via a CRI. The rate was calculated by use of $C_T \times Cl$, where Cl is the clearance (6.3 mL/min/kg) of fentanyl.[13]

Anesthetic recovery—Following measurements associated with the last dose of fentanyl, horses were moved to a padded equine anesthetic recovery stall. Recovery from anesthesia was always monitored directly by at least 2 of the investigators, who were not blinded regarding group assignments. Total anesthesia time, the times of several recovery events, and horse behavior were recorded. These included times to first movement, first attempts to attain sternal and standing positions, successful standing, and total recovery time. A subjective overall rating score of excellent, good, fair, or poor was assigned to each horse.[14,15] As soon as possible after the horse stood, a venous blood sample was collected for analysis of plasma fentanyl concentrations and its primary metabolite (PMA).[13] Venous blood was also collected at 1 hour and 1, 2, and 3 days after anesthesia for serum biochemical analyses.

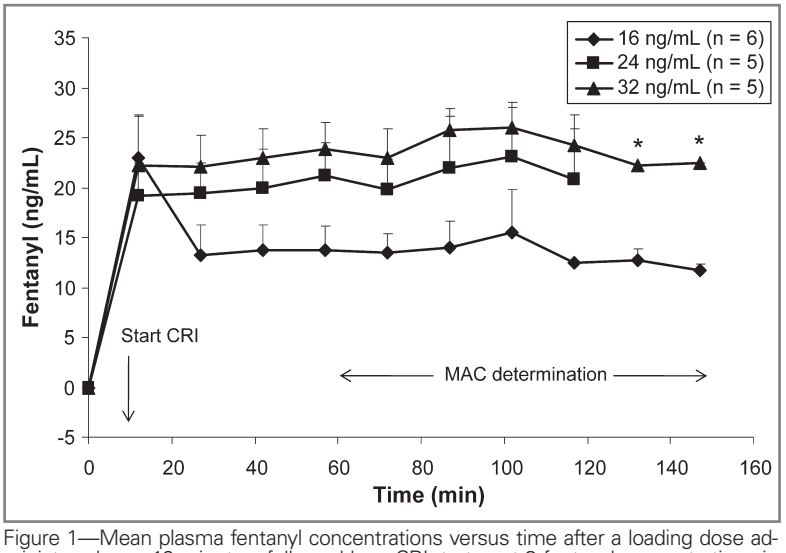

Figure 1—Mean plasma fentanyl concentrations versus time after a loading dose administered over 12 minutes, followed by a CRI, to target 3 fentanyl concentrations in horses for determination of MAC of isoflurane. *n = 1 horse. Error bars represent SD.

Determination of plasma fentanyl concentrations—Right external jugular venous blood samples were collected immediately before each bolus fentanyl administration, at the conclusion of the bolus administration, every 15 minutes during the fentanyl infusion, and immediately upon standing (postrecovery sample). Samples were collected via a syringe and transferred to tubes containing sodium heparin. Samples were centrifuged for 10 minutes, and plasma was stored at –20°C until analyzed for fentanyl and PMA concentrations. Fentanyl and PMA concentrations were determined by use of a described method via liquid-chromatography–mass spectrometry.[13]

Statistical analysis—Data were grouped and are expressed as mean ± SD values. Statistical analyses were performed to assess the effects of fentanyl concentration on the MAC of isoflurane. The effects of fentanyl concentration on temperature, PCV, TP concentration, Pa_{O_2}, Pa_{CO_2}, and arterial pH were also evaluated. The data from the MAC experiments were analyzed as an unbalanced mixed-model ANCOVA[g] in which the subject was a random effect, the target fentanyl concentration was a fixed effect, and the percentage error in attempting to achieve that C_T was a covariate. Post hoc comparisons were based on comparisons of the least squares means for the different target fentanyl concentrations. Considering the method of defining MAC and its associated variability, a variation of MAC between –8% and +8% was considered normal variation for interpretation of these experiments. For HR, SAP, MAP, and DAP, an additional categorical variable (stimulus) was added to the mixed-effect model. Significance was set at $P < 0.05$.

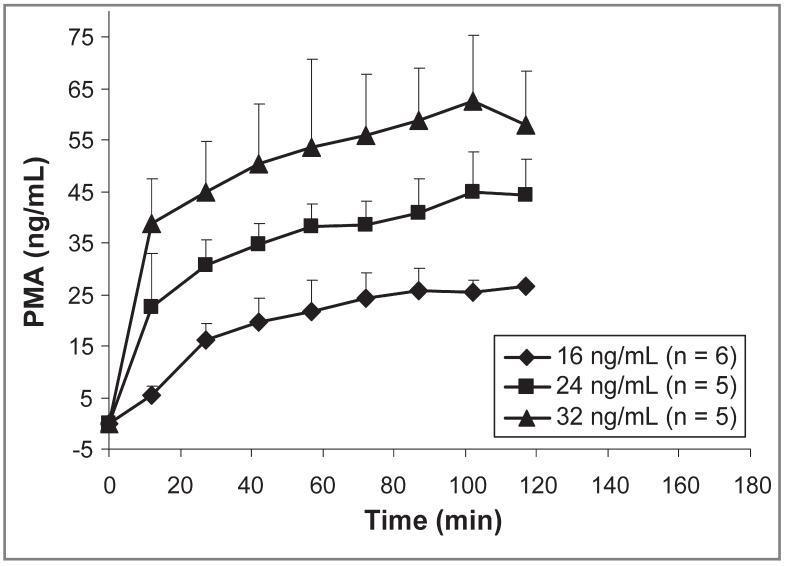

Figure 2—Mean plasma concentrations for PMA, the major metabolite of fentanyl, during fentanyl CRI in horses. Data were incomplete beyond 120 minutes and are not included. Error bars represent SD.

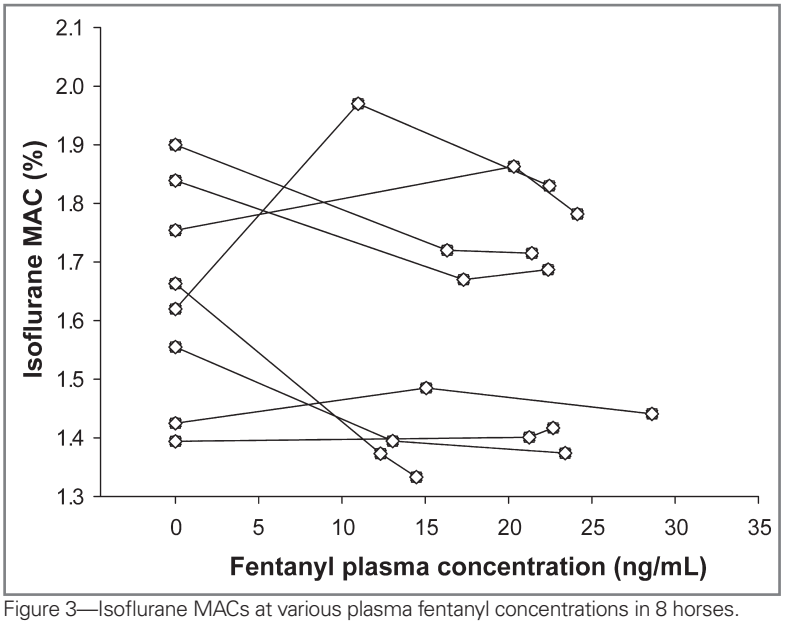

Figure 3—Isoflurane MACs at various plasma fentanyl concentrations in 8 horses.

Results

Plasma fentanyl concentration—Total time of fentanyl administration was 253 ± 11 minutes. Fentanyl was administered to each horse on the basis of randomly assigning 2 of the 3 target plasma concentrations of 16 (n = 6), 24 (5), and 32 (5) ng/mL. The fentanyl loading doses administered were 4.2, 6.2, and 8.3 µg/kg for target plasma concentrations of 16, 24, and 32 ng/mL, respectively, and the fentanyl infusion rates were 0.10, 0.15, and 0.2 µg/kg/min for target plasma concentrations of 16, 24, and 32 ng/mL respectively. The total amount of fentanyl administered was 8.5 ± 1.8 mg, 10.6 ± 2.2 mg, and 14.0 ± 2.5 mg for target plasma concentrations of 16, 24, and 32 ng/mL, respectively. Plasma fentanyl concentrations versus time during the relatively constant level of isoflurane anesthesia were determined (**Figure 1**). Plasma concentrations were steady for each horse at each C_T, but actual plasma fentanyl concentrations were less than C_T; that is, 13.9 ± 2.6 ng/mL, 20.1 ± 3.6 ng/mL, and 24.1 ± 2.4 ng/mL for the target concentrations of 16, 24, and 32 ng/mL, respectively. Fentanyl was rapidly metabolized as indicated by the plasma metabolite (PMA) concentrations, which quickly exceeded parent compound concentrations (**Figure 2**).

MAC—Baseline MAC for isoflurane was 1.64 ± 0.2%. The change in isoflurane MAC caused by increasing plasma concentrations of fentanyl, for individual horses, was determined (**Figure 3**). In 4 horses, MAC decreased from 9% to 18% (target plasma fentanyl concentrations of 16, 24, and 32 ng/mL); 3 horses had no change (ie, the change in these horses was +1.4 to +6.3% at target plasma fentanyl concentrations of 24 and 32 ng/mL); and in 1 horse, MAC increased by 21% (target plasma fentanyl concentration, 16 ng/mL). The directional changes in MAC were consistent in individual horses, but the magnitude of the change was not necessarily dose related for an individual horse.

Mean change in MAC relative to measured plasma fentanyl concentration was determined (**Figure 4**). Overall, isoflurane MAC decreased by 3.2% and 6.2% and increased by 1.2% for plasma fentanyl concentrations of 13.9, 20.1, and 24.1 ng/mL, respectively. Data for the present study and another study[11] were compared (**Figure 5**). A 9% difference in the effect on MAC was determined for the overlapping fentanyl concentration of 16 ng/mL between the 2 studies.

Physiologic responses—Temperature, PCV, TP concentration, $Paco_2$, and arterial pH did not change during the course of the study. Cardiopulmonary and temperature data were obtained just prior to noxious stimulation at each fentanyl concentration (**Table 1**). Heart rate did not change with stimulus or fentanyl administration. Systolic arterial pressure did not change with stimulation in the 0 and 32 ng/mL target fentanyl concentration groups; however, significant changes were detected between pre- and poststimulation values for target fentanyl concentrations of 16 and 24 ng/mL (**Figure 6**). Systolic arterial pressure poststimulation values were significantly different from baseline for all 3 fentanyl administrations.

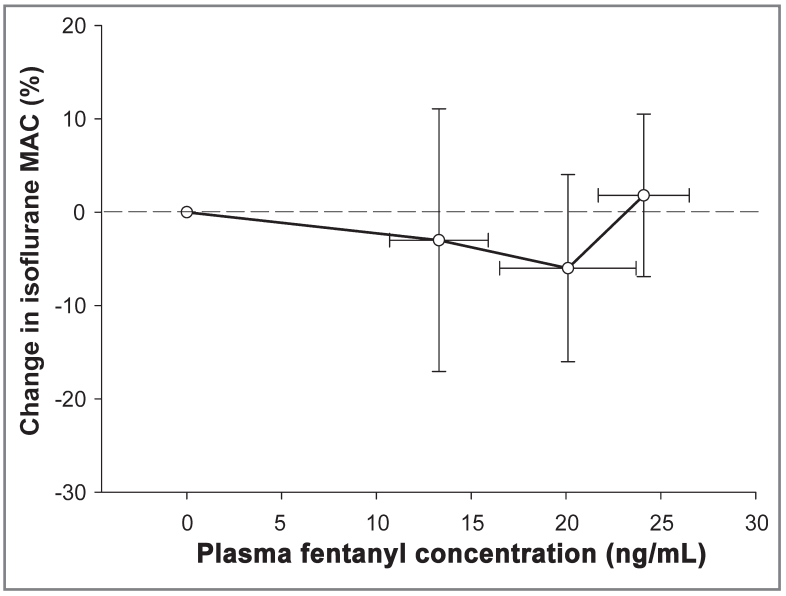

Figure 4—Mean ± SD percentage change in isoflurane MAC at 3 plasma fentanyl concentrations (mean ± SD) in 8 horses.

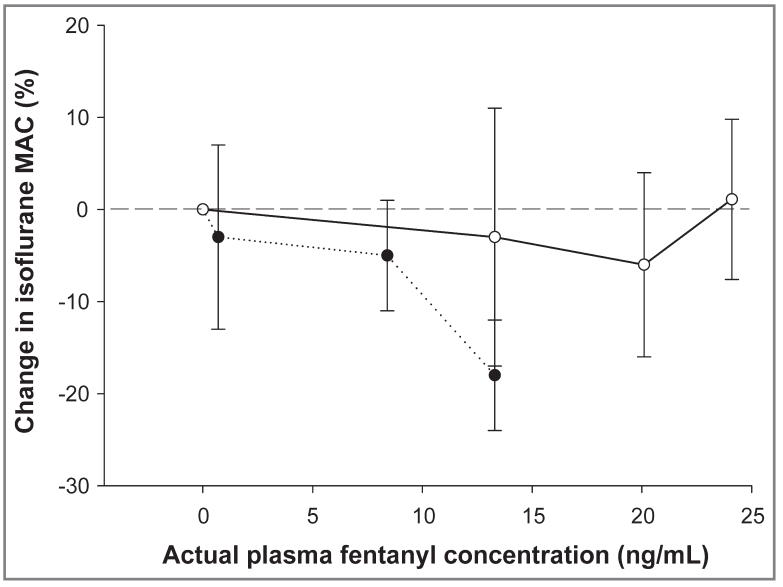

Figure 5—Mean ± SD percentage change in isoflurane MAC at various plasma fentanyl concentrations in 8 horses (white circles) and in a similar study (black circles).[11]

Table 1—Mean ± SD values of physiologic variables in 8 isoflurane-anesthetized horses at mean measured plasma fentanyl concentrations of 0, 13.9, 20.1, and 24.1 ng/mL.

Variable	0 ng/mL (n = 8)	13.9 ng/mL (n = 6)	20.1 ng/mL (n = 5)	24.1 ng/mL (n = 5)
Pao_2 (mm Hg)	316 ± 86	370 ± 100	358 ± 118	265 ± 70
$Paco_2$ (mm Hg)	48.6 ± 8.8	48.0 ± 2.2	46.0 ± 3.9	47.0 ± 3.3
Arterial pH	7.35 ± 0.07	7.40 ± 0.03	7.38 ± 0.03	7.39 ± 0.03
Temperature (°C)	37.3 ± 0.5	37.3 ± 0.6	37.4 ± 0.4	37.6 ± 0.7
PCV (%)	38 ± 4	36 ± 7	37 ± 6	37 ± 4
TP (mg/dL)	6.1 ± 0.4	5.8 ± 0.4	5.8 ± 0.4	5.6 ± 0.1

Recovery behavior—Total anesthesia time, determined as the time from a horse's first breath of isoflurane to the time the breathing circuit was disconnected from the tracheal tube, was 480 ± 18 minutes. Times to first movement, first attempts to sternal and standing positions, and successful standing were 10 ± 2 minutes, 19 ± 3 minutes, 48 ± 12 minutes, and 55 ± 10 minutes, respectively. Recovery behavior was variable with horses in the 32 ng/mL group and included highly undesirable, potentially injurious excitatory behavior. For example, those horses often attempted to rise faster and, after standing, circled frantically in both directions and usually fell several times. A subjective overall recovery rating of good (n = 3 horses), fair (3), or poor (2), but never excellent, was assigned to each horse at the conclusion of recovery from anesthesia (**Table 2**). Recovery plasma fentanyl concentrations immediately after standing were 4.1 ± 1.5 ng/mL and 6.7 ± 2.2 ng/mL for horses receiving a second target plasma fentanyl concentration of 24 and 32 ng/mL, respectively. Plasma fentanyl concentrations immediately prior to transport to the recovery stall as well as immediately upon standing as they relate to quality of recovery were determined. Gastrointestinal sounds in all quadrants and appetite were absent or decreased for 24 to 48 hours after anesthesia in all horses. A period of no production of feces was followed by production of loose feces (cow-like feces) in the first 12 hours after recovery. Serum SDH and bilirubin concentrations were significantly increased at 1 and 2 days after anesthesia. Serum CK and AST activities were also increased from baseline for up to 3 days after anesthesia (**Table 3**).

Discussion

The expectations of the present study were to verify a decrease in isoflurane MAC in horses via concurrent IV administration of the potent, short-acting opioid fentanyl at a dose previously reported to do so.[11] Furthermore, 2 additional doses were used to test the hypothesis that a progressive further reduction in MAC would occur with increased fentanyl doses. However, results of this study failed to support these expectations.

In this study, fentanyl was administered to isoflurane-anesthetized horses by first giving a fentanyl load-

ing dose over 12 minutes followed by a fentanyl CRI. The protocol for fentanyl administration was similar to the one used by Thomasy et al,[11] from this laboratory. Different horses of similar characteristics and source were used for the present study. As in the previous study, plasma fentanyl concentrations in the present study were stable over the time of administration (Figure 1) and values were slightly less than target plasma concentrations (13.9 ± 2.6 ng/mL, 20.1 ± 3.6 ng/mL, and 24.1 ± 2.4 ng/mL for C_T of 16, 24, and 32 ng/mL). In both the present and the previous study,[11] loading and infusion doses were calculated on the basis of previous fentanyl pharmacokinetic studies in isoflurane-anesthetized horses.[13] However, in the study of Thomasy et al,[11] the pharmacokinetic values for each horse were used to calculate administered fentanyl doses, whereas in the present study, previously reported mean values[13] were used. This difference in methodology did not appear to account for the discrepancy between C_T and actual concentrations; the mean plasma fentanyl concentration reached for the 16 ng/mL target group in the Thomasy study[11] was 13.3 ± 6.6 ng/mL, a value nearly identical to the 13.9 ± 2.6 ng/mL measured in the present study. The reasons for failure to reach or maintain C_T are likely multifactorial. In addition to individual animal variability, the potential for opioids, especially at high doses, to cause sympathetic stimulation[7,10] in horses might help explain our findings. Our data suggested that, as the dose of fentanyl was increased, there was an increase in sympathetic stimulation. For example, SAP values after stimulation were significantly different at all plasma fentanyl C_T, compared with baseline (0 ng/mL fentanyl) poststimulation values. This along with individual animal variability could account for differences in cardiac output, volume of distribution, and Cl. Method of administration of the loading dose may also have played a role in the difference between observed and targeted plasma concentrations. Because the loading dose was calculated by use of V_{dss} as opposed to volume of distribution for the central compartment, we elected to administer this over the course of 12 minutes in an effort to minimize adverse effects. At the end of administration of the 16 ng/mL loading dose, plasma fentanyl concentrations exceeded the C_T, but were not sustained during the CRI. At target concentrations of 24 and 32 ng/mL, the difference between observed and C_T widened. In part, this might have been the result of drug clearance continuing (concen-

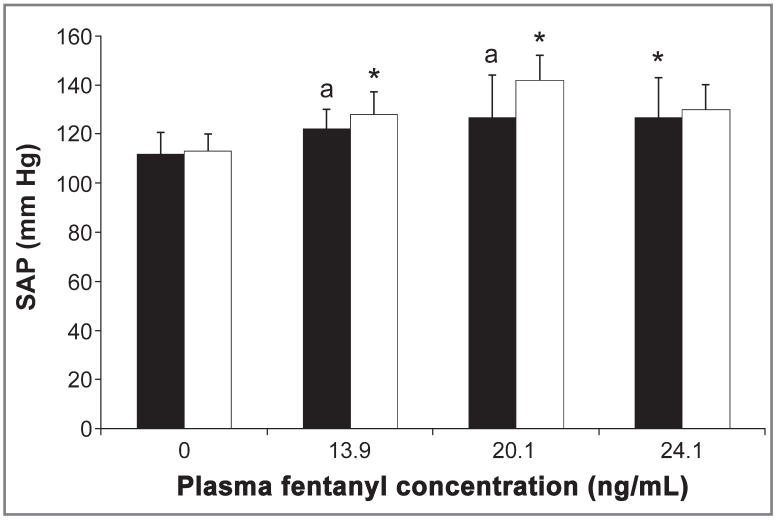

Figure 6—Mean SAP in 8 isoflurane-anesthetized horses immediately before (black bars) and after (white bars) noxious stimuli at mean plasma fentanyl concentrations of 0, 13.9, 20.1, and 24.1 ng/mL. [a]Significant ($P < 0.05$) difference between pre- and poststimulus values for a given fentanyl concentration. *Significant ($P < 0.05$) difference between poststimulation value and baseline poststimulation value (0 ng of fentanyl/mL). Error bars represent SD.

Table 2—Distribution of subjective estimates of recovery quality in 8 horses anesthetized with isoflurane and fentanyl. Horses are grouped on the basis of the change in MAC of isoflurane in response to fentanyl administration. Values in parentheses represent plasma fentanyl concentrations immediately prior to transport to the recovery stall at the end of anesthesia.

		Quality of recovery		
MAC	No. of horses	Good	Fair	Poor
Decrease	4	2 (25.5 ng/mL, 13.4 ng/mL)	1 (24.8 ng/mL)	1 (22.9 ng/mL)
No change	3	1 (23.4 ng/mL)	2 (25.6 ng/mL, 29.0 ng/mL)	0
Increase	1	0	0	1 (22.4 ng/mL)

Table 3—Mean ± SD values of serum biochemical analyses in 8 horses before (baseline) and after (postrecovery) anesthesia with isoflurane.

			Postrecovery			
Variable	Reference range	Baseline	1 day	2 days	3 days	4 to 5 days
AST (U/L, 37°C)	168–494	240 ± 46	407 ± 318	842 ± 356	1,053 ± 577	778 ± 442
CK (U/L, 37°C)	119–287	229 ± 68	2,066 ± 1,399	3,039 ± 1,276	1,520 ± 758	547 ± 313
ALP (U/L, 37°C)	86–285	106 ± 17	100 ± 41	130 ± 23	136 ± 16	129 ± 10
Total bilirubin (mg/dL)	0.5–2.3	2.0 ± 0.9	3.0 ± 1.6	5.0 ± 0.7	3.6 ± 1.6	2.5 ± 1.3
SDH (U/L, 37°C)	0–8	4.1 ± 1.7	13.9 ± 9.7	1.1 ± 0.2	1.8 ± 0.8	2.2 ± 0.9
BUN (mg/dL)	12–27	21 ± 1	21 ± 1	20 ± 3	15 ± 3	14 ± 4
Creatinine (mg/dL)	0.9–2.0	1.2 ± 0.1	1.5 ± 0.4	1.1 ± 0.2	1.0 ± 0.1	1.0 ± 0.2

Reference ranges are from the Clinical Pathology Laboratory, Veterinary Medical Teaching Hospital, University of California-Davis.

trations declining) as the CRI for the previous target was discontinued while the loading dose for the step up in concentration was administered. Additionally, loading dose for each C_T was calculated on the basis of predicted (vs actual) concentrations resulting in a relative underdose of drug. For example, when stepping up from 16 to 24 ng/mL, the loading dose was based on the difference between these 2 values (or 8 ng/mL $\times$ V_{dss}). However, the true difference would have been between 24 and 13.9 ng/mL (or 10.1 $\times$ V_{dss}).

Plasma concentrations of PMA, the major metabolite of fentanyl,[13] were also monitored throughout the course of the study (Figure 2). The plasma concentration of PMA increased over time and was directly related to the dose of fentanyl administered (ie, concentrations of PMA continued to increase at higher doses of fentanyl). We do not expect PMA to have had any important functional activity in the horses.[16]

Thomasy et al[11] detected a reduction in the MAC of isoflurane at plasma concentrations of 13.3 ng/mL (C_T of 16 ng/mL). However, in the present study, at mean plasma fentanyl concentration of 13.9 ng/mL, we found no consistent change in the MAC of isoflurane. In the present study, changes in MAC for horses in the 16 ng/mL target group ranged from –15.4% to +21.6%. At plasma concentrations near our C_T of 16 ng/mL, only 4 of the 8 horses had decreased MAC. Given that the same experimental protocol was used in each study, this suggested that the difference in results was attributable to variability in the pharmacodynamics of fentanyl among horses. More focused study of this point will improve our present understanding.

Overall, fentanyl caused a reduction in isoflurane MAC in 4 of the 8 horses and no change in 3. One horse in this study had a 22% increase in the MAC of isoflurane at a plasma fentanyl concentration of 11.0 ng/mL and a 12.9% increase when the fentanyl concentration was 22.5 ng/mL. A second horse had a 17% decrease in the MAC of isoflurane at a plasma fentanyl concentration of 12.3 ng/mL and a 20% decrease at a concentration of 14.5 ng/mL. The lack of a consistent correlation between plasma fentanyl concentrations and changes in isoflurane anesthetic requirement was consistent with similar observations following morphine administration to isoflurane-anesthetized horses reported by Steffey et al.[7]

Horses were mechanically ventilated to prevent hypercapnia, which could have an effect, either directly or indirectly, on MAC. With IPPV, ventilation was maintained normally throughout the course of the study. The Pa_{O_2} values did vary somewhat for individual horses and among the horses we studied; however, this is not unexpected among horses selected from a general population. It is interesting to note that, without explanation, reductions in Pa_{O_2} from earlier values were especially noteworthy in some individuals at higher plasma fentanyl concentrations. However, more important, Pa_{O_2} was always > 100 mm Hg and therefore any changes in Pa_{O_2} that were noted would not be expected to influence anesthetic requirement.

A number of the horses in this study had clearly undesirable recovery behaviors (Table 2). However, there was no correlation between plasma fentanyl concentrations immediately prior to recovery and recovery quality. These behaviors may relate to normal individual variation in horse recovery patterns and residual CNS-stimulating effects of fentanyl because the responses were characteristic of horses with opioid stimulation.[7,10] These horses often tried to stand early during recovery and would circle frantically and fall numerous times when attempting to stand. These behaviors were consistent with behaviors associated with concomitant administration of morphine and isoflurane.[7] With time, during recovery, these horses had behaviors more characteristic of those described for horses recovering from only inhalation anesthesia.[17] The mean plasma fentanyl concentration immediately upon standing was 5.70 ± 2.25 ng/mL, which was higher than the value reported by Thomasy et al[11] (2.78 ± 1.47 ng/mL), when lower doses of fentanyl were administered. Furthermore, in the present study, a wider range of fentanyl concentrations was measured (2.80 to 10.05 ng/mL), compared with the previous study,[11] in which less variability in postrecovery fentanyl concentrations was observed. In the previous study, recovery behaviors were also more characteristic of those seen following recovery from inhalation anesthesia in the absence of adjuvant drugs. In the present study, immediately following recovery from anesthesia, all horses had signs typical of horses receiving large amounts of opioids, including decreased gastrointestinal sounds in all quadrants, decreased fecal output, and decreased appetite. Usually, upon return of fecal passage, feces were loose and unformed. These behaviors returned to normal over the course of 24 to 48 hours after anesthesia without specific intervention.

Clinical serum biochemical values were within reference ranges for all horses prior to commencement of this study. Indices of renal function (BUN and creatinine concentration) were within reference ranges following anesthesia. There was however, a significant increase in serum AST and CK activities (Table 3) in all horses. These enzymes increase in serum with the loss of cellular integrity of muscle fibers. In this study, increases in the activities of these enzymes were most likely indicative of sublethal muscle cell damage attributable either to the prolonged periods of recumbency or to trauma associated with attempts to stand during recovery from anesthesia. These findings are consistent with a previous report[18] of increased activities of CK and AST associated with prolonged isoflurane anesthesia in horses. In addition to its presence in muscle, AST is also found in large amounts in the liver and is often used as an indicator of cellular integrity. The higher values for some horses, compared with others, can be correlated with the quality of recovery. Relative to baseline preanesthetic values, serum bilirubin concentrations were increased at 1 to 2 days after anesthesia, likely related to postanesthetic transient inappetance, which occurred in all the horses.

The findings of the present study were in agreement with results of a study[7] of other opioids in horses but in disagreement with previous results assessing the anesthetic-sparing effect of fentanyl on isoflurane,[11] likely because of variability among individual horses. Furthermore, some recovery behaviors were undesir-

able and characteristic of excitatory behaviors observed following administration of opioids to unanesthetized horses. Overall, results of the present study did not support the routine use of fentanyl as an anesthetic adjuvant in adult horses.

a. LB-2 CO_2 and anesthetic analyzer, Sensormedics Corp, Anaheim, Calif.
b. Model P23D, Division of Mark IV Industries, Oxnard, Calif.
c. Model 7 polygraph, Grass Instruments, Quincy, Mass.
d. Model AB330, Radiometer America, Cleveland, Ohio.
e. YSI-Tele-thermometer, model 43, Yellow Springs Instrument Co, Yellow Springs, Ohio.
f. Modified Mark 14, Bird Corp, Palm Springs, Calif.
g. SAS Institute Inc, Cary, NC.

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