Effects of desflurane and mode of ventilation on cardiovascular and respiratory functions and clinicopathologic variables in horses

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Objective—To quantitate the effects of desflurane and mode of ventilation on cardiovascular and respiratory functions and identify changes in selected clinicopathologic variables and serum fluoride values associated with desflurane anesthesia in horses.

Animals—6 healthy adult horses.

Procedure—Horses were anesthetized on 2 occasions: first, to determine the minimum alveolar concentration (MAC) of desflurane in O_2 and second, to characterize cardiopulmonary and clinicopathologic responses to 1X, 1.5X, and 1.75X desflurane MAC during both controlled and spontaneous ventilation.

Results—Mean ± SEM MAC of desflurane in horses was 8.06 ± 0.41%; inhalation of desflurane did not appear to cause airway irritation. During spontaneous ventilation, mean $Paco_2$ was 69 mm Hg. Arterial blood pressure, stroke volume, and cardiac output decreased as the dose of desflurane increased. Conditions of intermittent positive pressure ventilation and eucapnia resulted in further cardiovascular depression. Horses recovered quickly from anesthesia with little transient or no clinicopathologic evidence of adverse effects. Serum fluoride concentration before and after administration of desflurane was below the limit of detection of 0.05 ppm (2.63μM/L).

Conclusions and Clinical Relevance—Results indicate that desflurane, like other inhalation anesthetics, causes profound hypoventilation in horses. The magnitude of cardiovascular depression is related to dose and mode of ventilation; cardiovascular depression is less severe at doses of 1X to 1.5X MAC, compared with known effects of other inhalation anesthetics under similar conditions. Desflurane is not metabolized to an important degree and does not appear to prominently influence renal function or hepatic cellular integrity or function. (*Am J Vet Res* 2005;66:669–677)

Desflurane is an inhalation anesthetic that has been approved for use in human patients in the United States for a decade. Despite some favorable physical characteristics that may facilitate advances in the anesthetic management of horses, reports of desflurane action in equids are limited. In 1995 and 1996, Clarke et al[1,2] and Jones et al[3] reported their observations of Welsh Mountain Ponies in which anesthesia had been induced with xylazine and ketamine and maintained with desflurane. A year later, Tendillo et al[4] described the anesthetic potency (represented by the **minimum alveolar concentration [MAC]**) of desflurane in otherwise unmedicated horses. The purpose of the study reported here was to further quantitate the effects of desflurane and mode of ventilation on cardiovascular and respiratory functions and identify changes in selected clinicopathologic variables and serum fluoride values associated with desflurane anesthesia in horses. Because the potency of desflurane in the horses that are included in an investigation importantly impacts study results, we first determined MAC for desflurane in each horse and used this individualized value for subsequent evaluations.

Materials and Methods

Horses—Six healthy horses (3 females and 3 geldings) that were not receiving medications were included in the study. In this group of horses, the mean ± SEM age was 5.5 ± 0.6 years (range, 3 to 7 years) and the mean weight was 468 ± 28 kg (range, 357 to 542 kg). The group was comprised of 3 Standardbreds, 2 Thoroughbreds, and 1 Appaloosa.

Study conditions—The study was approved by the Animal Use and Care Administrative Advisory Committee of the University of California's Davis campus. The horses were anesthetized on 2 occasions at least 14 but no more than 42 days apart. The first time each horse was anesthetized, the MAC of desflurane was determined, and during the second anesthetic episode, cardiovascular and respiratory system

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variables were assessed at 1.0X, 1.5X, and 1.75X desflurane MAC (dose order was randomized in each horse). The desflurane MAC determined for each horse was used to define the absolute desflurane concentration (**volume percent [vol%]**) at each step rather than having all horses receive the same 3 absolute desflurane concentrations. Responses were recorded during conditions of controlled and then spontaneous ventilation at each multiple of MAC.

Anesthetic technique and general methods of study followed procedures used in the investigation of inhalation anesthetics previously described in reports[5-7] from this laboratory. Briefly, anesthesia was always induced in the morning after food (but not water) had been withheld from the horses for 8 to 12 hours. Preanesthetic medication was not administered, and the horses received only desflurane in O_2 for induction and maintenance of anesthesia. Desflurane was administered first via a face mask and then via an oroendotracheal tube (internal diameter, 30 mm) connected to a standard, semiclosed anesthetic circle system designed for use in large animals, which included a 30-L rebreathing bag contained in a locally fabricated bag-in-barrel system. This system permitted controlled or spontaneous ventilation without changing circuit components. Desflurane was delivered from an agent-specific precision vaporizer[a] with a minimum O_2 delivery rate of 6 L/min. After induction of anesthesia, the horses were positioned in left lateral recumbency on a thick foam pad on a movable cart.

Inspired and end-expired gas concentrations of O_2, CO_2, and desflurane were analyzed by use of polarographic[b] and infrared[c] gas analyzers. Each day, before anesthesia was induced in the horses, the analyzers were calibrated with multiple known standards; the calibration was frequently monitored throughout the study day. Measured inspired and end-expired gas concentrations were corrected mathematically according to gas-specific calibration curves that spanned the measured concentrations. Esophageal temperature was monitored by use of a calibrated thermistor.[d] Lactated Ringer's solution was infused at a rate of 3 mL/kg/h via a catheter positioned in the left medial saphenous vein. The urinary bladder was catheterized to maintain an empty bladder during anesthesia. A catheter was percutaneously positioned either in the facial (MAC determinations) or carotid (dose-response evaluations) arteries for collection of blood samples and cardiovascular measurements. During the dose-response evaluations, a catheter was also percutaneously positioned in the main trunk of the pulmonary artery via the right jugular vein.

During spontaneous ventilation, a calibrated pneumotachograph[e] positioned in the air inlet-outlet of a bag-in-barrel system was used to record respiratory rate and gas flow (including peak inspiratory and expiratory gas flows) according to a previously described technique.[6] Expired minute volume was obtained by electronic integration of the expired flow signal recorded on the pen writer.[f] The tidal volume was calculated, and both minute and tidal volumes were mathematically corrected from ambient conditions to that of body temperature, pressure, and water vapor saturated (BTPS). The mean of analyses of 5 consecutive breaths was recorded.

Blood was anaerobically obtained at various times from either the arterial or both the arterial and pulmonary artery catheters for P_{O_2}, P_{CO_2}, and pH analyses[g] (including assessment of Pa_{O_2}, Pa_{CO_2}, arterial pH, partial pressure of O_2 in pulmonary artery [mixed venous] blood, partial pressure of CO_2 in pulmonary artery [mixed venous] blood, pH value of pulmonary artery [mixed venous] blood, and arterial blood base balance). On occasions when blood was withdrawn from both the arterial and pulmonary artery catheters, samples were collected simultaneously. Blood was slowly drawn into syringes containing heparin over a period of 1 minute, and analysis was usually performed immediately. In the few instances when immediate analysis was not possible, the capped syringes were stored in ice and analysis was performed within 15 minutes of sample collection. Resultant values were corrected to the horse's body temperature. Arterial base balance was calculated by the blood gas machine on the basis of a nomogram for human blood. The Hct and plasma protein concentration (via refractometer) were also determined from these blood samples.

Heart rate and rhythm data were obtained from a base-apex ECG tracing on a pen recorder. Direct arterial systolic and diastolic blood pressure measurements were made on the same pen recorder via a strain gauge-transducer attached to the arterial catheter (filled with saline [0.9% NaCl] solution containing heparin). The strain gauge was calibrated at the beginning of each study day by use of a mercury column, and during the assessments, it was positioned level with the midportion of the sternum. The mean arterial blood pressure signal was calculated electronically. Similar to carotid pressure measurements, systolic and diastolic pulmonary artery pressures were measured and mean pulmonary artery pressure was obtained by electronic dampening of the pulmonary artery pressure signal. The carotid and pulmonary arterial catheters were also necessary to measure cardiac output. The cardiac output was determined by the indocyanine green dye dilution technique according to the technique used in this laboratory for previous studies[6,7] in horses. A 12.5-mg dose of green dye was injected via the pulmonary artery catheter for each cardiac output determination. The emerging dye curve was obtained from blood samples collected via the carotid artery catheter that were analyzed by a calibrated densitometer.[h] Cardiac output was then hand-calculated from the resultant dye curves. The mean value of at least 2 cardiac output determinations (but usually 3) that did not differ by > 10% was recorded for each anesthetic level. The green dye was always injected at the beginning of expiration and never during a breath administered via positive pressure ventilation (ie, the ventilator was briefly turned off for the time necessary to measure cardiac output). Stroke volume, total peripheral resistance, and cardiac output referenced to body mass (cardiac output/kg [cardiac index]) were computed by use of standard equations.

The protocol used in this investigation of desflurane closely followed methods that were used in a recent study[8] of the action of sevoflurane in horses.

MAC measurements—The MAC of desflurane that prevented movement in response to at least 60 seconds of electrical stimulation (50 V; 5 cycles/s; 10 milliseconds in duration[i]) of oral mucous membranes was determined for each horse during spontaneous ventilation according to techniques commonly used in this laboratory.[5] Alveolar desflurane concentration was determined from hand-drawn, end-tidal gas samples, and end-tidal concentration was held constant for at least 20 minutes prior to stimulation. The reported MAC was the mean of at least 3 MAC determinations for each horse. After MAC was determined, administration of desflurane was discontinued and the horses recovered from anesthesia in a padded recovery stall without adverse incidence.

Dose-response cardiovascular measurements—At least 14 (but no more than 42) days following MAC determination, the horses were again similarly anesthetized. During the 30 minutes following anesthetic induction, horses were prepared for evaluation while spontaneously breathing. After 45 to 50 minutes of anesthesia, the inspired desflurane concentration was either increased or decreased to attain the first previously assigned level. The doses of desflurane evaluated were 1.0X, 1.5X, and 1.75X MAC, as determined for each

horse; the randomized order in which these doses were evaluated in each horse had been determined prior to assessment of the first horse. The reasons for selection of these doses were similar to the reasons for dose selection in a recent study[8] of sevoflurane action in horses. A dose of 1.75× MAC desflurane was selected as the maximal dose because personal experience and published information[9] suggested that at a greater dose (eg, 2× MAC) of desflurane, all horses would likely not survive for a sufficient period to allow evaluation. After 1 hour of anesthesia (timed from a horse's first breath of desflurane), **intermittent positive pressure ventilation (IPPV)** was instituted to attain and maintain a $Paco_2$ of 45 mm Hg and a peak inspiratory pressure of 18 to 22 cm H_2O (conditions of controlled ventilation). Mechanical breaths were provided by a pressure-cycled ventilator[j] that powered the bag-in-barrel system. The peak inspiratory pressure was measured with a calibrated strain-gauge transducer attached to a port at the proximal (mouth) end of the endotracheal tube. Constant conditions of IPPV and end-tidal desflurane concentration were maintained for 20 minutes before obtaining cardiopulmonary measurements. The sequence in which measurements were made was established for all horses as follows: collection of blood samples, measurement of vascular pressures, measurement of respiratory gas flow and pressure, and assessment of cardiac output. At the completion of these measurements, the end-tidal anesthetic level was maintained but IPPV was discontinued. Spontaneous ventilation began after a brief time as $Paco_2$ increased to breathing threshold. After at least 10 minutes of constant conditions (ie, anesthetic dose, breathing conditions, and $Paco_2$ value), measurements were repeated. At the end of measurements during spontaneous ventilation, IPPV was similarly reinstituted and a new anesthetic level established. Once the appropriate desflurane dose and $Paco_2$ value were attained, conditions were again maintained constant for 20 minutes before the set of measurements during controlled ventilation was obtained. This was similarly followed by maintenance of end-tidal dose of desflurane and reestablishment of conditions of spontaneous ventilation. After at least 10 minutes of constant conditions of spontaneous ventilation, measurements were repeated. When these measurements were completed, controlled ventilation was again started and the third and final anesthetic dose was established. After the appropriate period of constant conditions, measurements at this dose were similarly obtained during both controlled and spontaneous ventilation.

Recovery from anesthesia—After each of the 2 anesthetic episodes, the endotracheal tube was disconnected from the breathing circuit and each horse was moved to a padded recovery stall. Oxygen was insufflated via the endotracheal tube at a rate of 15 L/min. Each horse was monitored for signs of arousal, and the following data were recorded: time to first movement, time to tracheal extubation, time to first attempt to attain sternal recumbency, time to first attempt to stand, time of standing, number of attempts to attain sternal recumbency, and number of attempts to stand. Recovery was subjectively graded by one of the investigators (EPS) according to a previously described scheme.[10,11]

Collection and analysis of blood samples—Between 30 and 60 minutes before anesthesia for the dose-response evaluations, a sample of jugular venous blood was collected percutaneously from 5 of the 6 horses for serum biochemical and fluoride ion analyses (baseline values). Blood samples for analysis were also obtained after 2 hours of anesthesia; at the end of anesthesia (for serum fluoride ion analysis only); and at 1 hour and 1, 2, and 4 days after the horse recovered from anesthesia sufficiently to stand for serum fluoride ion analysis and measurement of other serum biochemical variables. Sera from these samples were obtained within 1 hour of venipuncture and stored at –20°C until analyzed (usually within a day but not later than 4 days after collection) by the Clinical Pathology Laboratory of the Veterinary Medical Teaching Hospital, University of California, Davis, via standard techniques for that laboratory. Serum samples were analyzed for aspartate transaminase; γ-glutamyltransferase; sorbitol dehydrogenase; alkaline phosphatase; and creatine kinase activities and concentrations of total bilirubin, direct bilirubin (from which indirect bilirubin concentration was calculated), BUN, creatinine, glucose, inorganic phosphorus, and calcium. Serum inorganic fluoride concentration was analyzed[k] as previously reported.[8]

Data analyses—Data were grouped, and the mean ± SEM values were calculated for cardiopulmonary, clinicopathologic, and recovery data. Repeated-measures ANOVA was used to test for differences on the basis of anesthetic dose and ventilation type. The raw and logarithmically transformed data were used for analyses of the serum biochemical and most of the cardiopulmonary data. The preanesthetic values were used as baseline values for assessment of the clinicopathologic analyses. When the treatment effects for the serum biochemical data were not normally distributed, a

Table 1—Mean ± SEM values of blood gas and pH variables, Hct, and plasma protein concentration in 6 horses anesthetized with 3 doses of desflurane in O_2 (1.0×, 1.5×, and 1.75× minimum alveolar concentration [MAC] of desflurane) under conditions of controlled or spontaneous ventilation.

	Controlled ventilation			Spontaneous ventilation		
Variable	**1.0× MAC**	**1.5× MAC**	**1.75× MAC**	**1.0× MAC**	**1.5× MAC**	**1.75× MAC**
Pao_2 (mm Hg)	277 ± 69	116 ± 33	181 ± 67	220 ± 54	95 ± 19	108 ± 11
$Paco_2$ (mm Hg)	44.8 ± 0.7	49.1 ± 1.3	46.4 ± 0.8	66.6 ± 5.8	70.3 ± 3.0	69.9 ± 2.7
pHa	7.40 ± 0.01	7.36 ± 0.01	7.38 ± 0.01	7.28 ± 0.03	7.25 ± 0.01	7.25 ± 0.01
Arterial base balance (mEq/L)	3.2 ± 0.9	2.0 ± 0.6	2.3 ± 0.4	3.2 ± 0.8	2.2 ± 0.6	2.5 ± 0.3
$Ppao_2$ (mm Hg)	40.3 ± 1.0	81.3 ± 48.3	32.9 ± 1.8	60.8 ± 17.6	64.4 ± 25.1	92.5 ± 51.2
$Ppaco_2$ (mm Hg)	51.3 ± 3.2	53.2 ± 4.9	55.1 ± 2.9	64.8 ± 6.8	72.6 ± 4.6	69.1 ± 6.4
pHpa	7.36 ± 0.02	7.31 ± 0.02	7.34 ± 0.01	7.29 ± 0.03	7.23 ± 0.01	7.25 ± 0.02
Hct (%)	37.8 ± 1.4	42.8 ± 1.3	41.2 ± 1.4	41.2 ± 2.0	46.5 ± 1.6	47.2 ± 0.9
Plasma protein (g/dL)	6.0 ± 0.1	5.9 ± 0.1	5.9 ± 0.1	6.1 ± 0.2	6.0 ± 0.2	6.1 ± 0.1
Esophageal temperature (°C)	37.0 ± 0.2	36.9 ± 0.3	36.9 ± 0.2	36.9 ± 0.3	36.9 ± 0.3	37.0 ± 0.2

pHa = Arterial pH. $Ppao_2$ = Partial pressure of O_2 in pulmonary artery (mixed venous) blood. $Ppaco_2$ = Partial pressure of CO_2 in pulmonary artery (mixed venous) blood. pHpa = pH value of pulmonary artery (mixed venous) blood.

Friedman repeated-measures ANOVA on rank was used. A paired *t* test was used to analyze anesthetic recovery data. Data are reported as mean values ± SEM; significance for all statistical tests was set at $\alpha = 0.05$.

Results

MAC measurements—Desflurane MAC was 8.06 ± 0.41%. At MAC, body temperature was 37.4°C, the inspired desflurane concentration was 8.34 ± 0.44%, and the ratio of alveolar to inspired concentration was 0.97. Total anesthesia time for the MAC determinations was 3.56 ± 0.15 hours.

Respiratory responses to changes in desflurane dose—During controlled ventilation, the peak inspiratory pressure was 19.7 ± 0.3 cm H_20. The $Paco_2$ was kept constant (**Table 1**), and the mean value at the 3 anesthetic doses evaluated was 46.8 ± 0.7 mm Hg. Blood gas and pH values were also measured during spontaneous ventilation. During spontaneous ventilation, values of $Paco_2$ did not change significantly with changes in anesthetic dose. The mechanics of breathing during spontaneous ventilation were assessed; values at 1.0X and 1.5X MAC were not significantly different, but at 1.75X MAC, respiratory frequency was significantly increased and tidal volume and peak expiratory flow were significantly decreased, compared with values at 1.0X MAC (**Table 2**). No horse became apneic at the doses of desflurane evaluated, and no signs of airway irritation (eg, coughing or abnormal amount or character of respiratory system secretions) were observed during either of the 2 anesthetic inductions or during anesthetic recovery.

Cardiovascular responses to changes in desflurane dose—Regardless the mode of ventilation, arterial blood pressure, stroke volume, and cardiac output in horses decreased as the dose of desflurane increased. Values of heart rate and total peripheral vascular resistance did not change. At a given MAC multiple of desflurane, systemic and pulmonary arterial blood pressures, stroke volume, and cardiac output values were always less during controlled ventilation than they were during spontaneous ventilation (**Tables 3 and 4**; **Figure 1**).

The third horse evaluated died suddenly at the end of the study day during completion of the final cardiac output measurement at steady-state conditions of 1.5X MAC and spontaneous ventilation. The sequence in which doses of desflurane were administered to this horse was 1.0X, 1.75X, and finally 1.5X MAC. Prior to death, the horse had no clinical signs of adverse effects associated with the depth of anesthesia; no life-threatening dysrhythmias were noted during the study or immediately before the asystole immediately preceding death. In this horse, values of physiologic variables obtained during spontaneous ventilation at 1.5X MAC and just prior to death included sys-

Table 2—Mean ± SEM values of respiratory variables in 6 horses anesthetized with 3 doses of desflurane in O_2 (1.0X, 1.5X, and 1.75X MAC) under conditions of spontaneous ventilation.

	Spontaneous ventilation		
Variable	**1.0X MAC**	**1.5X MAC**	**1.75X MAC**
Respiratory frequency (breaths/min)	4.0 ± 0.9	3.8 ± 0.5	6.4 ± 1.5*
V_t (L/breath, BTPS)	8.46 ± 1.36	8.38 ± 1.26	5.79 ± 0.88*
V_E (L/min, BTPS)	29.50 ± 5.64	29.41 ± 3.32	31.01 ± 2.07
Peak inspiratory gas flow (L/min)	387 ± 95	394 ± 73	323 ± 46
Peak expiratory gas flow (L/min)	500 ± 45	458 ± 36	408 ± 35*

*Value significantly ($P \leq 0.05$) different from 1.0X MAC value.
V_t = Tidal volume. V_E = Expired minute volume. BTPS = Value mathematically corrected from ambient conditions to that of body temperature, pressure, and water vapor saturated.

Table 3—Mean ± SEM values of cardiovascular variables in 6 horses anesthetized with 3 doses of desflurane in O_2 (1.0X, 1.5X, and 1.75X MAC) under conditions of controlled or spontaneous ventilation.

	Controlled ventilation			Spontaneous ventilation		
Variable	**1.0X MAC**	**1.5X MAC**	**1.75X MAC**	**1.0X MAC**	**1.5X MAC**	**1.75X MAC**
SAP (mm Hg)	97 ± 3	76 ± 5	65 ± 5	116 ± 4	91 ± 7	84 ± 5
DAP (mm Hg)	71 ± 3	50 ± 5	47 ± 4	81 ± 3	64 ± 7	59 ± 5
MAP (mm Hg)	80 ± 2	59 ± 5	53 ± 4	93 ± 3	73 ± 7	68 ± 5
HR (beats/min)	40.8 ± 2.3	41.0 ± 4.5	45.7 ± 3.4	43.4 ± 2.3	41.3 ± 4.4	46.1 ± 2.6
SV (mL/beat)	952 ± 256	688 ± 79	491 ± 107*	1010 ± 119	882 ± 103	743 ± 133
CO (L/min)	37.3 ± 8.7	27.5 ± 3.9	22.1 ± 3.7*	43.2 ± 4.5	35.8 ± 5.3	33.9 ± 6.0
CI (mL/kg/min)	77.4 ± 14.2	58.4 ± 7.7	45.0 ± 7.5*	93.2 ± 10.0	75.6 ± 10.5	70.7 ± 11.6
TPR (dynes·s/cm^5)	202 ± 30	185 ± 22	218 ± 34*	184 ± 25	174 ± 17	190 ± 36
SPAP (mm Hg)	31 ± 2	32 ± 1	31 ± 2	36 ± 3	38 ± 3	37 ± 2
DPAP (mm Hg)	27 ± 3	29 ± 2	28 ± 2	33 ± 4	34 ± 4	33 ± 3
MPAP (mm Hg)	26 ± 2	27 ± 1	26 ± 2	30 ± 2	30 ± 3	30 ± 1

*Value calculated from data for 5 horses.
SAP = Systolic blood pressure. DAP = Diastolic blood pressure. MAP = Mean arterial pressure. HR = Heart rate. SV = Stroke volume. CO = Cardiac output. CI = Cardiac index. TPR = Total peripheral resistance. SPAP = Systolic pulmonary artery pressure. DPAP = Diastolic pulmonary artery pressure. MPAP = Mean pulmonary artery pressure.

Table 4—Results of mixed model ANOVAs for cardiopulmonary data from 6 horses anesthetized with 3 doses of desflurane in O_2 (1.0X, 1.5X, and 1.75X MAC) under conditions of controlled or spontaneous ventilation.

	Significance of different factors			
Variable	**Ventilation**	***P* value**	**MAC**	***P* value**
SAP	SV > CV	< 0.001	1 > 1.5, 1.75	< 0.001
DAP	SV > CV	< 0.001	1 > 1.5, 1.75	< 0.001
MAP	SV > CV	< 0.001	1 > 1.5, 1.75	< 0.001
HR	—	NS	—	NS
SV	SV > CV	0.019	1, 1.5, 1.75	0.022
CO	SV > CV	0.013	1, 1.5, 1.75	0.005
CI	SV > CV	0.014	1 > 1.5, 1.75	0.003
TPR	—	NS	—	NS
SPAP	SV > CV	0.003	—	NS
DPAP	SV > CV	0.002	—	NS
MPAP	SV > CV	0.002	—	NS
Pa_{O_2}	CV > SV	0.020	—	NS
Pa_{CO_2}	SV > CV	< 0.001	—	NS
pHa	CV > SV	< 0.001	—	NS
Arterial base balance	—	NS		NS
Ppa_{O_2}	—	NS	—	NS
Ppa_{CO_2}	SV > CV	< 0.001	—	NS
pHpa	CV > SV	< 0.001	—	NS
Hct	SV > CV	< 0.001	1.75, 1.5 > 1	0.008
Plasma protein concentration	SV > CV	0.027	NS	
Temperature	—	NS	—	NS

The *P* values of the ventilation X MAC interaction for all variables were > 0.05.
SV = Spontaneous ventilation. CV = Controlled ventilation. NS = No significant difference. — = Data not shown because difference was not significant.
See Tables 1 and 3 for remainder of key.

tolic and mean arterial blood pressures of 72 and 58 mm Hg, respectively; cardiac output of 50 mL/min/kg; heart rate of 54 beats/min; and values of Pa_{O_2} and Pa_{CO_2} of 70 and 68 mm Hg, respectively. Results of a necropsy performed on this horse were not helpful in determining the cause of death. Because there were no other unusual circumstances (other than death) associated with the evaluation of this horse, exclusion of this horse's data from certain summarized study results could not be justified. Accordingly, the data reported are based on results from all 6 horses, except for analyses of events associated with recovery from anesthesia after each anesthetic episode and clinicopathologic variables.

Recovery from desflurane anesthesia—Anesthetic duration and recovery events following anesthesia were analyzed for both the MAC determination and dose-response portions of this study **(Table 5)**. Anesthetic conditions for the dose-response–related measurements were longer in duration and resulted in more desflurane exposure (given in MAC hours) and longer recovery times, compared with conditions associated with MAC determinations. Anesthetic time and recovery events associated with MAC determination for the horse that died were within the range of values obtained from the other 5 horses. Behavior during recovery from anesthesia was subjectively rated as being within the usual spectrum of behavior associated with horses that are recovering from only inhalation anesthesia (ie, no administration of peri- or immediate post-anesthetic adjuvant drugs). The recovery pattern for an individual horse was similar following both anesthetic protocols. Recoveries were subjectively graded as fair to good for 2 horses (largely on the basis of vigorous head slapping during their attempts to move from lateral to sternal recumbency early in the recovery period), very good for 1 horse, and excellent (represented by a slow, deliberate rise to stand) for the remaining 3 horses. Recovery from anesthesia after MAC determination in the horse that died was graded as excellent.

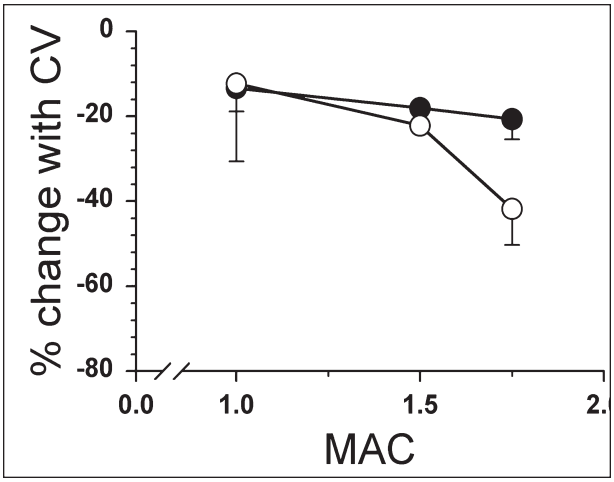

Figure 1—Mean ± SEM percentage change in mean arterial blood pressure (closed circles) and cardiac output per kilogram (open circles) associated with the use of controlled ventilation (CV), compared with values associated with the use of spontaneous ventilation, in 6 horses receiving 3 doses of desflurane (1.0X, 1.5X, and 1.75X minimum alveolar concentration [MAC] of desflurane).

An interesting observation during recovery from anesthesia was that the horses usually began to object to the presence of the endotracheal tube shortly before standing. Objection usually took the form of vigorous chewing of the endotracheal tube. In addition, they would also frequently swallow or shake or strangely posture their head and neck (or combinations of these actions). Coughing or other signs of airway irritation

Table 5—Summary (mean ± SEM) of duration of anesthesia and events during recovery from anesthesia for 5 horses anesthetized with desflurane in O_2 on 2 occasions for MAC determinations and dose-response evaluations.

	Anesthetic episode	
Event	**MAC determination**	**Dose-response evaluation**
Anesthetic duration (h)*	3.67 ± 0.13	5.33 ± 0.21†
MAC hours (h)‡	3.86 ± 0.13	7.26 ± 0.33†
Time to first movement (min)§	3.00 ± 0.32	8.00 ± 0.95†
Time to first attempt to attain sternal posture	4.60 ± 1.03	14.20 ± 1.88†
Time to first attempt to stand	10.60 ± 1.72	19.60 ± 0.68†
Time to standing	12.00 ± 1.05	22.20 ± 1.16†
No. of attempts to maintain sternal posture	2.40 ± 0.60	4.40 ± 1.72
No. of attempts to stand	1.40 ± 0.25	2.00 ± 0.78
Time to extubation	7.20 ± 1.02	18.80 ± 1.66†

*Time from first breath of desflurane to time of endotracheal tube disconnection from the anesthetic breathing circuit †Value significantly ($P < 0.05$) different from that associated with MAC determination. ‡Time summary of periods at multiples of MAC. §Times represent the time from disconnect from the anesthetic breathing circuit and cessation of the stable level of anesthesia.

Table 6—Serum biochemical variables (mean ± SEM) in 5 horses before and at intervals after anesthesia with 3 doses of desflurane in O_2 (1.0X, 1.5X, and 1.75X MAC) in a dose-response evaluation.

			Time after standing during recovery from anesthesia			
Analyte	**Reference range***	**Baseline value**	**1 h**	**1 d**	**2 d**	**4 d**
AST (U/L [37°C])	138–409	216 ± 9	220 ± 18	470 ± 89†	481 ± 107†	435 ± 102†
CK (U/L [37°C])	119–287	169 ± 16	707 ± 158†	2,480 ± 1,154†	1,243 ± 593†	541 ± 171†
ALP (U/L [37°C])	86–285	93 ± 10	98 ± 10	111 ± 14†	115 ± 12†	108 ± 11†
TBil (mg/dL)	0.5–2.3	2.6 ± 0.3	2.7 ± 0.3	2.8 ± 0.3	2.7 ± 0.3	2.3 ±0.5
IBil (mg/dL)	0.3–1.7	2.5 ± 0.3	2.6 ± 0.3	2.7 ± 0.3	2.6 ± 0.3	2.1 ± 0.5
GGT (U/L [37°C])	8–22	12.0 ± 0.6	10.6 ± 0.7	12.2 ± 0.9	12.6 ± 0.8	12.4 ± 0.8
SDH (U/L [37°C])	0–8	4.0 ± 0.3	16.0 ± 2.8†	5.0 ± 0.9	3.2 ± 0.4	3.2 ± 0.2
BUN (mg/dL)	12–27	21.8 ± 0.6	28.4 ± 0.9†	22.6 ± 1.2	21.6 ± 0.6	19.0 ± 1.1
Creatinine (mg/dL)	0.9–2.0	1.12 ± 0.04	2.48 ± 0.22†	1.12 ± 0.07	1.04 ± 0.04	1.06 ± 0.08
Glucose (mg/dL)	59–122	94 ± 2	215 ± 23†	101 ± 5	94 ± 5	97 ± 5
Inorganic phosphorus (mg/dL)	2.1–4.7	4.5 ± 0.4	6.5 ± 0.3†	1.9 ± 0.1†	3.3 ± 0.1†	4.7 ± 0.2
Calcium (mg/dL)	12.1–13.7	11.2 ± 0.2	9.9 ± 0.3†	11.6 ± 0.1	12.1 ± 0.2†	12.2 ± 0.2†

*Reference ranges used by the Clinical Pathology Laboratory, Veterinary Medical Teaching Hospital, University of California, Davis. †Value significantly ($P \leq 0.05$) different from baseline value.
AST = Aspartate aminotransferase. CK = Creatine kinase. ALP = Alkaline phosphatase. TBil = Total bilirubin. IBil = Indirect bilirubin. GGT = γ-glutamyltransferase. SDH = Sorbitol dehydrogenase.

were not typically part of this behavior. Once extubated, the horses no longer displayed aversive behavior.

Results of analyses of blood samples obtained before and after anesthesia for dose-response evaluations—As a result of the death of 1 horse near the conclusion of the dose-response evaluation, results of blood analyses were summarized on the basis of data obtained from only 5 horses (**Table 6**). Immediately following the dose-response studies (ie, 1 hour after cessation of anesthesia), serum sorbitol dehydrogenase activity and BUN and glucose concentrations were increased from baseline values. By the next day (day 1 after anesthesia), these variables had returned to baseline values. Immediately after anesthesia, serum inorganic phosphorus concentration was increased and serum calcium concentration was decreased, compared with baseline values. By day 1 after anesthesia, serum concentration of calcium had returned to the baseline value but that of phosphorus was now significantly less than the baseline value. On day 4 after anesthesia, serum phosphorus concentration had returned to the baseline value. The serum aspartate transaminase, creatine kinase, and alkaline phosphatase activities transiently increased at day 1 after anesthesia before returning toward or to baseline over the next few days. Four of the 5 horses had notable increases, especially in serum creatine kinase activity. Serum inorganic fluoride concentration was always below the level of detection at all time points (ie, < 2.63μM/L).

Discussion

Desflurane MAC determined in the horses of the present study was 8.06 ± 0.41 vol%. This value is approximately 15% greater than that reported previously.[2,4] One explanation for this difference in findings is that it is largely a result of normal biological variation. For example, for horses evaluated in our laboratory, the halothane MAC has ranged from 0.88 ± 0.03 vol%[5] to 0.97 to 1.05 vol%[12] (a difference of approx 12%) and similarly, the isoflurane MAC has ranged from 1.31 ± 0.07 vol%[5] to 1.64 ± 0.05 vol%[13] (a difference of > 20%). We would expect the desflurane MAC to be similarly variable. Indeed, reports[14,15] of desflurane MAC in rats from another laboratory differ by 20%. However, with regard to desflurane MAC, methodological differences between the present study and those reported previously could also contribute to some but likely not all of the difference in results. For example, in a study[2] of 6 Welsh Mountain Ponies (ie,

not horses), the mean ± SD desflurane MAC was 7.0 ± 0.85 vol%; however, on the basis of indirect evidence that has been previously reported, a major difference in the MAC of inhalation anesthetics between ponies and horses is considered unlikely. In support of this opinion, Matthews et al[16] reported a halothane MAC in ponies of 0.93 to 0.97 vol%; these values lie within the range of halothane values at MAC reported for horses. However, a more important consideration is the administration of adjuvant drugs to equids used in studies determining anesthetic potency. In the study involving Welsh Mountain Ponies,[2] anesthesia was induced with xylazine (1.1 mg/kg, IV) and ketamine (2.2 mg/kg, IV); the dose of xylazine used would be expected to decrease MAC for at least 3 hours in horses.[13] Ketamine has also been shown to decrease MAC in horses.[17] The duration of the effect of this dose of ketamine (alone or in combination with xylazine) on MAC in horses is unknown; the effect of ketamine alone on halothane MAC is prolonged in rats.[18] Consequently, taking all these facts into consideration, the MAC value reported for Welsh Mountain Ponies likely underestimates the true MAC for desflurane in healthy, otherwise unmedicated equids.

Tendillo et al[4] evaluated desflurane in otherwise unmedicated horses and reported a mean ± SD desflurane MAC of 7.6 ± 0.3 vol% (it should be noted that based on the individual horse values, the correct value for the SD value is given in Table 1 of their report as opposed to the value noted in the report narrative and abstract); this value is within 6% of the finding of the present study. However, the value for MAC reported by Tendillo et al was determined under conditions at Madrid, Spain, and that location is about 635 m (2,100 ft) above sea level. Correction of their reported value of 7.6 vol% to sea level conditions (because Davis, Calif, is near sea level) yields a value of 7.02 vol%; again, there is a difference of approximately 15% between this corrected value and the desflurane MAC determined in our study (8.06 vol%). Although there are some methodological differences between the study of Tendillo et al and our investigation that may account for an underestimation of desflurane MAC in the former, any such influences are considered small. Having taken these influences into account, it is assumed that most of the difference in findings is related to normal biological variability among horses.

In the present study, the values of $Paco_2$ indicated that ventilation was maintained constant and within the desired range during conditions of controlled ventilation. Not surprisingly, during conditions of spontaneous ventilation, $Paco_2$ at all of the 3 MAC multiples was greater than that expected for an awake horse breathing O_2 at sea level.[6] The magnitude of $Paco_2$ at 1.0× MAC desflurane agreed closely with results obtained from horses similarly anesthetized with isoflurane.[5,7] When the dose of desflurane was increased to 1.5× MAC, there was a small, consistent, but nonsignificant, additional increase in $Paco_2$, which suggests that desflurane is at least as much of a respiratory depressant as isoflurane. These results are in qualitative agreement with the results of a study in ponies by Clarke et al.[1] The results of the present study unexpectedly differed quantitatively from those in ponies in that a significant increase in $Paco_2$ was noted when the desflurane dose given to ponies was increased.

In humans, desflurane is a ventilatory depressant and the degree of ventilatory depression observed is comparable to that associated with isoflurane[19]; desflurane depresses ventilation in humans primarily by reducing tidal volume because the respiratory frequency does not increase sufficiently to compensate. In the horses of our study, we also detected a decrease in tidal volume during exposure to the highest concentration of desflurane but respiratory frequency increased sufficiently to keep minute ventilation constant and prevent an increase in $Paco_2$.

In the absence of other drugs, surgical stimulus, or disease, desflurane caused a dose-related decrease in arterial blood pressure, stroke volume, and cardiac output in horses. These effects are qualitatively similar to the actions of other inhalation anesthetics in horses,[5,7,8] desflurane in other species,[20-23] and desflurane in ponies given adjuvant anesthetic drugs.[1] In addition to anesthetic dose, the magnitude of the effect of desflurane in the horses of our study was further influenced by mode of ventilation; mechanical ventilation increased the depressant effect of a given dose of desflurane. For example, mean arterial blood pressure and cardiac output per kilogram at 1.5× MAC desflurane during conditions of spontaneous ventilation were not significantly different (by paired *t* test) in magnitude from values obtained at 1.0× MAC desflurane during conditions of controlled ventilation.

In comparison with findings of studies[5-8] of other inhalation anesthetics in unmedicated horses, other cardiovascular responses of horses to desflurane that were detected in our study are noteworthy. First, the magnitude of cardiac output per kilogram in spontaneously breathing horses at all 3 concentrations of desflurane in O_2 (but also at 1.0× MAC during controlled ventilation) was near values reported for awake horses that are breathing O_2.[6] This is in distinction to the more depressant effect on cardiac output by other inhalation anesthetics in horses, especially at anesthetic conditions > 1.0× MAC. Second, systemic vascular resistance in the horses anesthetized with desflurane in our study was less than that determined in awake and isoflurane- or halothane-anesthetized horses. However, like actions of other inhalation anesthetics in horses, no significant change in vascular resistance accompanied changes in anesthetic dose. Third, the Hct value increased with increasing dose of desflurane and was greatest during spontaneous ventilation in the horses of our study. We presume that this occurred as a result of splenic contraction (plasma protein concentration did not change) in response to increased sympathetic tone; however, beyond this, we have no further explanation.

In the horses of the present study, recovery from anesthesia occurred rapidly following discontinuation of desflurane administration. Compared with the first episode of anesthesia (the MAC determination), recovery times were significantly greater for the second episode of anesthesia (the dose-response evaluation),

presumably because this period of anesthesia was longer in duration (about 1.7 times as long as the first period of anesthesia) and the horses were exposed to higher desflurane concentrations. Both factors contribute to a greater MAC-hour exposure. Our usual practice following inhalation anesthesia is to extubate horses after they stand. It is interesting that during recovery from desflurane anesthesia, the horses in the present study usually would not tolerate retention of the tracheal tube during the later phases of lateral or sternal recumbency. We presume that this behavior was related to the low blood gas partition coefficient of desflurane that fosters its rapid elimination from the body and permits early conscious recognition of the orotracheal tube as an undesirable foreign body.

Results of the present study indicated that quantitative changes in selected serum analytes were either absent or small in horses that were anesthetized for > 5 hours (attaining profound levels of desflurane anesthesia at times) without surgical intervention. Results of indices of renal function and hepatic cellular integrity and function in our study were very similar to data reported for horses that underwent isoflurane anesthesia of similar duration.[24] The similarity in results from these 2 investigations adds further support to the suggestion that the transient clinicopathologic changes detected are generalized effects of prolonged anesthesia in horses rather than a specific effect of a particular agent (in this instance, desflurane). However, in the evaluation of desflurane-anesthetized horses, there were 2 analytes for which the changes in concentration were more extreme than would be expected following, for example, isoflurane anesthesia. Immediately following anesthesia, serum glucose concentration was double the baseline value; by the next day (day 1 after anesthesia), the concentration had returned to the baseline value. The data are too limited to speculate whether this is an indicator of stressful circumstances occurring during anesthesia or recovery from desflurane, but this interesting finding warrants further investigation in studies of desflurane. The other analyte of interest was creatine kinase. An increase in serum creatine kinase activity from the baseline value was detected at 1 hour after anesthesia, and a peak activity was detected by 1 day after anesthesia. After this time point, the serum creatine kinase activity decreased; by 4 days after anesthesia (the last day of sample collection), the value was less than that at 1 hour after anesthesia. This change in serum creatine kinase activity is similar to the pattern noted after isoflurane anesthesia, except that on first inspection of the data, the magnitude of change associated with desflurane anesthesia seems greater. When allowances are made for differences in techniques used by investigators in the same laboratory for completion of analyses in isoflurane- and desflurane-anesthetized horses (in studies performed in the late 1970s vs present day) and the different temperatures for which the test results were reported (25° vs 37°C), any difference in serum creatine kinase results between the 2 studies is small and considered unimportant. Overall, the results of the present study support the view that a small to moderate increase in serum creatine kinase activity is a common consequence of anesthesia, recumbency, and recovery from anesthesia (ie, events associated with return to a standing posture) in horses.

It has long been known that the inhalation anesthetic agents are not chemically inert. There is potential for various degrees of metabolism, and the metabolites formed may be toxic. In the development of new inhalation anesthetic agents, those that are not metabolized or are metabolized to a lesser extent than existing agents are considered an improvement. Desflurane is resistant to metabolism in humans,[25] rats,[26] and young pigs.[27] However, species differences exist with regard to the extent that metabolism of desflurane may occur. Although there is evidence that horses and humans degrade inhalation anesthetics to a similar extent,[8,28,l] specific data about desflurane breakdown by horses are lacking. In the present study, plasma fluoride ion concentration was assessed as an indication of the metabolism of desflurane by horses. However, in desflurane-anesthetized horses, changes in this variable were undetectable; this finding suggests that desflurane is resistant to breakdown in horses, as it is in humans, rats, and young swine. Furthermore, these data also suggest that any desflurane-induced release of fluoride ion into the bloodstream is of such low magnitude that there is no concern for associated renal damage in horses, even following prolonged desflurane anesthesia.

a. Tec 6 vaporizer, Omeda Inc, Madison, Wis.
b. Model OM-11, Sensormedics Corp, Anaheim, Calif.
c. Model LB-2 CO_2 and anesthetic analyzers, Sensormedics Corp, Anaheim, Calif.
d. YSI Tele-thermometer model 43, Yellow Springs Instrument Co, Yellow Springs, Ohio.
e. Fleisch No. 4, Instrumentation Associates Inc, New York, NY.
f. Model 7 polygraph, Grass Instruments, Quincy, Mass.
g. Model ABL 330, Radiometer America, Cleveland, Ohio.
h. Lyons Medical Instrument Co, Van Nuys, Calif.
i. Model S44 stimulator, Grass Instruments, Quincy, Mass.
j. Modified Bird Mark 9 ventilator, Bird Corp, Palm Springs, Calif.
k. Analysis of blood samples for inorganic fluoride performed by the Toxicology Laboratory, California Animal Health and Food Safety, University of California, Davis, Calif.
l. Rice SA, Steffey EP. Metabolism of halothane and isoflurane in horses (abstr). *Vet Surg* 1985;14:76.

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