Effects of xylazine hydrochloride during isoflurane-induced anesthesia in horses

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Objective—To quantitate dose- and time-related anesthetic-sparing effects of xylazine hydrochloride (XYL) during isoflurane-induced anesthesia in horses and to characterize selected physiologic responses of anesthetized horses to administration of XYL.

Animals—6 healthy adult horses.

Procedure—Horses were anesthetized 2 times to determine the minimum alveolar concentration (MAC) of isoflurane in O_2 and to characterize the anesthetic-sparing effect (MAC reduction) after IV administration of XYL (0.5 and 1 mg/kg of body weight, random order). Selected measures of cardiopulmonary function, blood glucose concentrations, and urinary output also were measured during the anesthetic studies.

Results—Isoflurane MAC (mean ± SEM) was reduced by 24.8 ± 0.5 and 34.2 ± 1.9% at 42 ± 7 and 67 ± 10 minutes, respectively, after administration of XYL at 0.5 and 1 mg/kg. Amount of MAC reduction by XYL was dose- and time-dependent. Overall, cardiovascular and respiratory values varied little among treatments. Administration of XYL increased blood glucose concentration; the magnitude of change was dose- and time-dependent. Urine volume increased but not significantly.

Conclusions and Clinical Relevance—Administration of XYL reduced the anesthetic requirement for isoflurane in horses. The magnitude of the decrease is dose- and time-dependent. Administration of XYL increases blood glucose concentration in anesthetized horses in a dose-related manner. (*Am J Vet Res* 2000;61:1225–1231)

Administration of α_2-adrenergic agonists causes sedation and analgesia. They are commonly administered to horses as adjuvants for general and regional anesthesia. The ability of various α_2-agonists to decrease requirements for primary anesthetic agents has been documented in a number of species, including rats,[1-3] dogs,[4-7] rabbits,[8] and humans.[9,10] Because of the prominence of α_2-agonists in the anesthetic management of horses, its impressive ability to reduce anesthetic requirement in other species, and the limited amount of objective data on anesthetic potency in horses,[11,a] the study reported here was conducted. The study focused on the effects of **xylazine hydrochloride (XYL)**; currently, XYL is 1 of the α_2-agonists most commonly used in clinical management of horses in the United States. The objective of the study was to provide a dose-related measure of the degree of the anesthetic-sparing effect of XYL and the time course of that effect. Circumstances also provided opportunity to briefly characterize, at a relatively constant dose in a light plane of general anesthesia, some measures of cardiopulmonary performance, blood glucose concentration, and urinary flow.[b] The study was conducted in horses anesthetized with isoflurane, using change in **minimum alveolar concentration (MAC)** of isoflurane as a measure of analgesia and changing anesthetic requirements.[12]

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Materials and Methods

Horses—Healthy adult horses of various breeds (mostly Thoroughbreds) that weighed (mean ± SEM) 505 ± 11 kg were obtained from a pool of horses donated to the university and maintained at our equine research facilities. Six horses (1 female and 5 castrated males; 5.2 ± 0.6 years old) were included in the study. The study protocol was approved by an institutional animal care and use committee.

The 6 horses were each anesthetized 2 times to enable us to characterize the anesthetic-sparing effect of 2 dosages of XYL (0.5 and 1.0 mg/kg of body weight, IV). We chose these dosages on the basis that it would bracket those in common clinical use as well as because of results of prior studies.[13,14] Half of the horses were randomly selected to initially receive the low dose, whereas the other half received the high dose. Feed was withheld for 12 hours before induction of anesthesia, but water was always available.

Study conditions—Anesthesia was induced in nonmedicated horses, using only isoflurane in O_2, as described elsewhere.[15] The inhaled anesthetic was delivered to each horse via a mask connected to an anesthetic circle system developed for use in large animals. Orotracheal intubation (26 or 30 mm, ID, cuffed endotracheal tube) was performed when anesthetic depth was suitable (10 to 15 minutes after start of induction). Following intubation, horses were positioned in left lateral recumbency on a thickly padded cart and transported to the laboratory (approx 1 to 2 minutes) without being disconnected from the breathing circuit. After arriving in the laboratory, each horse was prepared for study during the remainder of the first hour of anesthesia. A calibrated thermistor probe[c] was positioned in the nasopharynx to measure body temperature. A base-apex lead ECG[d] was used to monitor heart rate and rhythm. An 18-gauge 2-inch catheter[e] was inserted percutaneously into the right carotid artery, which had been surgically elevated to a position just beneath the skin ≥ 2 months before the start of this study. The catheter was connected to a strain gauge[f] positioned level with the sternum. The strain gauge was calibrated at the beginning of each experimental day, using a mercury column. Another catheter was inserted into the main pulmonary

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artery via the right jugular vein for similarly derived pressure measurements. 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 after the first breath of isoflurane (ie, start of anesthetic induction).

End-expired gas samples were obtained by intermittent manual collection from a nylon catheter positioned near the caudal tip of the tracheal tube. Isoflurane was measured with an infrared gas analyzer[g] that was calibrated before the start of each study against multiple tank standards.[h] Calibration checks also were made throughout each study day. Final isoflurane values were corrected according to calibration curves obtained at the beginning of each study day. Concentrations of O_2 and CO_2 also were intermittently monitored by use of calibrated polarographic[i] and infrared[j] analyzers, respectively. In addition, we used a locally modified calibrated mass spectrometer[k] system[16,17] as a secondary monitor to continuously verify the inspired and expired concentrations of O_2, N_2, CO_2, and isoflurane.

Horses were allowed to breathe naturally (ie, spontaneous ventilation), except for periodic deep sighs accomplished by compression of the breathing circuit reservoir bag. A calibrated pneumotachograph[l] was positioned in the air inlet-outlet of a bag-in-barrel system that replaced the breathing bag of the anesthetic breathing circuit. This system then was used to record respiratory rate.[18]

Determination of minimum alveolar concentration— Approximately 1 hour after anesthetic induction, determination of control MAC was begun. Standard techniques that have been previously reported by our laboratory group were used.[12,19] Briefly, end-tidal anesthetic concentration was maintained constant for at least 20 minutes, and anesthetic step changes of approximately 10% but not greater than 20% of the previous concentration were used. A response was judged to be positive when a purposeful movement (usually lifting or twisting of the head or movement of a limb) was detected in response to electrical stimulation (≤ 60 seconds) of oral mucous membranes (noxious stimulus; 50 V, 5 Hz, 10 milliseconds in duration[d]). The MAC was determined 3 times for each horse, and the mean value was recorded. Following these control measurements, XYL then was injected IV during a period of 1 minute, and MAC was determined again multiple times during the next 3 to 5 hours. To accomplish this, the usual technique to determine MAC was modified as follows.[20-22] End-expired isoflurane concentration was rapidly reduced at the time of XYL injection to a concentration that was estimated, on the basis of prior experience, to be just slightly greater than the concentration that would allow a positive response to noxious stimulation. This concentration was maintained constant, and a response or lack of response to a noxious stimulus was recorded over time. A period of approximately 20 minutes at a constant dose of isoflurane was maintained after that change in concentration before a noxious stimulus was applied again. This was done to minimize presumed alveolar-arterial anesthetic differences. After a positive response to noxious stimulation, the end-expired isoflurane concentration was rapidly increased to a new concentration that produced a negative response to the same noxious stimulus. The new concentration was maintained constant at each value until a positive response again was obtained, and the process was repeated again. In this phase of the study, the noxious stimulus was applied approximately every 20 minutes, unless the horse's behavior to a stimulus predicted a closely pending positive response. In such cases, noxious stimulation was applied at intervals of 5 to 10 minutes to improve precision for measurement of the time of events. At each new end-expired isoflurane concentration, the mean of the last minute for which a negative response was obtained and the time of purposeful movement in response to noxious stimulation was calculated. At least 4 MAC points were obtained for each horse following XYL injection. The initial determination of MAC after injection of XYL did not take place until approximately 40 minutes after injection to ensure a uniform response. We reasoned that during the initial 40 minutes after injection, blood concentrations of injectable drug would be rapidly changing as a result of drug redistribution, and, thus, accuracy of data for anesthetic-sparing effect would be unacceptably compromised. We continued MAC determination until MAC returned to within ≤ 10% of the control MAC value or approximately 200 minutes had elapsed after injection of XYL. In some cases in which total anesthesia time was not considered excessive for a particular horse or out of proportion to the general group, we continued MAC determination beyond the general guidelines to verify consistency of return to control values and to ensure that MAC did not increase beyond control values.

Cardiopulmonary measurements—Using recorded values, blood pressure in the carotid and pulmonary arteries and heart rate were determined 30 and 60 seconds preceding application of a noxious stimulus. To minimize differences attributable to the effect of differing isoflurane concentrations, values at those paired times used to determine the MAC were averaged, and the resultant mean values then were considered as the heart rate and blood pressure at MAC. Values for respiratory frequency were obtained in a similar manner.

Blood gas analysis—Arterial blood samples were collected in heparinized syringes before anesthetic induction periodically before (at or near MAC of isoflurane) XYL injection and 1, 2, 3, 4, 6, 8, 10, 12, 18, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes after XYL injection. Within a few minutes after collection, each sample was analyzed[m] to determine Pa_{O_2}, Pa_{CO_2}, and pH_a. Measured results were corrected on the basis of the horse's rectal (awake) or pharyngeal (anesthetized) temperature.

Blood samples were collected from the jugular vein of horses before induction of anesthesia, 1 hour and 1 day after recovery from anesthesia, and during anesthesia (immediately before administration of XYL and 12, 30, 60, 120, and 240 minutes after XYL administration). Serum was harvested from these samples within 1 hour after collection and stored at –20 C (short term) or –70 C (long term) until analyzed for glucose concentration, which was usually performed the next day but always was performed within a few days after collection.[n]

Urine measurements—The urinary bladder was aseptically catheterized during the first hour of anesthesia, and urine was collected before and during 2-hour periods after XYL injection. Urine was collected passively by gravity or actively into a closed-system collector, and it was measured by use of a calibrated burette at appropriate times. Emptying of the urinary bladder always was checked by air injection and a quantitative air evacuation technique; in some instances, direct examination of the bladder was accomplished via transrectal palpation.

Statistical analysis—Values were expressed as mean ± SEM, except when indicated. Inferential statistics included 1-way and 2-way repeated-measures ANOVA, and associated post hoc Bonferroni (multiple comparisons vs control values) and Tukey (used for multiple pairwise comparisons) tests and paired *t*-tests were used, as appropriate, to compare cardiopulmonary, blood gas, and urine data associated with administration of XYL. Raw cardiopulmonary data and logarithmically transformed data for glucose concentration and

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urine indices were used in the analyses. Perianesthetic preadministration data were considered baseline values for blood gas, urine, and blood glucose concentration analyses. A value of $P < 0.05$ was considered significant.

Results

Anesthesia—Total duration of anesthesia was 7.42 ± 0.16 hours. All horses recovered from anesthesia without clinically important consequences. During anesthesia, horses received supplemental fluids IV at the rate of 2.74 ± 0.07 ml/kg/h. In addition, horses received periodic small-volume boluses of fluid to flush catheters and to ensure fluid lines remained patent and free of blood.

Isoflurane MAC and XYL-induced changes in isoflurane MAC—Mean of all 12 determinations of isoflurane MAC in the 6 horses was 1.64 ± 0.05%. The control MAC for isoflurane for each dosage was determined (**Table 1**) as well as the maximal measured changes and time references following IV injections of XYL. The difference in control MAC for a particular horse within a drug dosage (ie, comparing baseline MAC with MAC after administration of a low and high dose) ranged from 0.01 to 0.24% (mean, 0.12%) isoflurane. Mean maximal reduction in MAC caused by XYL that we were able to measure with this technique was 25 and 34% for 0.5 and 1.0 ml/kg, respectively. These reductions were detected at a mean of 42 and 67 minutes after XYL injection; the difference between these times was significant. The MAC data from specific horses were grouped according to similar times and summarized. Graphic summaries of the rate of change in return of MAC to, or nearly to, control values after XYL administration were evaluated (**Fig 1**). Values after XYL administration differed significantly on the basis of dose ($P = 0.015$ for a specific time) and time ($P = 0.007$ for a specific dose of XYL).

Cardiopulmonary responses—Three data points were summarized for heart rate, mean arterial blood pressure, mean pulmonary artery blood pressure, and respiratory frequency for approximately the same time during anesthesia for each dosage of XYL (1 point before XYL administration and 2 points after XYL administration). Only heart rate and mean arterial blood pressure for the dose of 1.0 mg/kg differed significantly before and after XYL administration (**Table 2**).

Blood gas analyses—Arterial blood gas values for these horses prior to anesthesia were considered to be normal, and they were similar in magnitude during anesthesia immediately prior to XYL administration (**Table 3**). For example, the pooled (mean ± SEM) Pa_{O_2} was 100.8 ± 9.6 mm Hg, and pooled Pa_{CO_2} was 44.8 ± 0.7 mm Hg, respectively, prior to anesthesia.

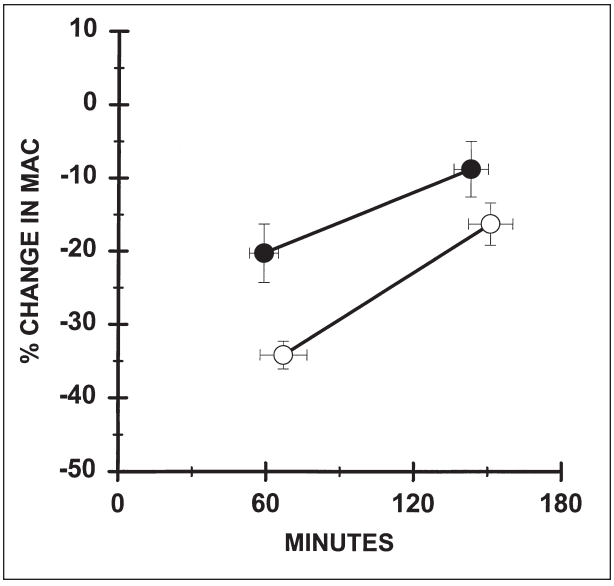

Figure 1—Effects of xylazine hydrochloride administration on mean ± SEM minimum alveolar concentration (MAC) for isoflurane in 6 horses. Notice the reduction in isoflurane MAC at each dose of xylazine (● = 0.5 mg/kg of body weight; ○ = 1.0 mg/kg). Values differ significantly ($P = 0.02$) on the basis of dose (for a specific time) and time (for a specific dose). Time 0 = Time of xylazine administration.

A similar consistency was evident during anesthesia and O_2 breathing immediately before XYL administration. For example, Pa_{O_2} and Pa_{CO_2} immediately before XYL administration was 250 ± 47.5 and 65.2 ± 3.8 mm Hg, respectively. Following XYL administration, Pa_{O_2} and Pa_{CO_2} did not change significantly, regardless of time or dosage, from values obtained immediately before XYL administration.

Blood glucose concentrations—Blood glucose concentration increased, but not significantly, following induction of anesthesia with isoflurane. A nonsignificant increase in blood glucose concentration, compared with values for horses before anesthesia and for baseline anesthesia, was evident after administration of XYL at both dosages (**Table 4**). A significant increase in glucose was detected 12 minutes after administration of XYL at both dosages. The magnitude of increase 12 minutes after injection was similar for both dosages of XYL, but thereafter it was dose-related. For both dosages, values remained significantly increased for 2 hours after XYL injection.

Table 1—Minimum alveolar concentration (MAC) for isoflurane in 6 horses before and after IV administration of xylazine hydrochloride

	Control period		Maximum change in MAC after administration of drug		
Xylazine hydrochloride (mg/kg of body weight)	MAC	Pharyngeal temperature (C)	Time (min)	Change in MAC (%)	Pharyngeal temperature (C)
0.5	1.62 ± 0.07	37.3 ± 0.3	42 ± 7*	−24.8 ± 2.4	37.2 ± 0.3
1.0	1.67 ± 0.07	37.6 ± 0.2	67 ± 10*	−34.2 ± 1.9	37.9 ± 0.3

Values are expressed as mean ± SEM.
*Values differ significantly ($P < 0.05$).

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Table 2—Data for cardiopulmonary variables before and at 2 time points after administration of xylazine in 6 horses anesthetized with isoflurane, with anesthetic doses at all time points similarly potent (equivalent to isoflurane MAC 1.0)

	0.5 mg/kg			1.0 mg/kg		
Variable	**Before**	**After**		**Before**	**After**	
Time after administration	NA	59 ± 6	155 ± 16	NA	66 ± 9	129 ± 10
HR (beats/min)	38 ± 2	35 ± 2	37 ± 2	42 ± 3	36 ± 2*	37 ± 2*
MAP (mm Hg)	89 ± 4	90 ± 4	82 ± 3*	92 ± 7	89 ± 6	78 ± 4*
MPAP (mm Hg)	27 ± 4	27 ± 3	25 ± 4	31 ± 5	30 ± 2	27 ± 3
f (breaths/min)	5 ± 1	5 ± 1	5 ± 1	5 ± 1	7 ± 1	5 ± 2

Values are mean ± SEM.
*Value differs significantly ($P < 0.05$) from the value before administration at the same dose. NA = Not applicable. HR = Heart rate. MAP = Mean arterial blood pressure. MPAP = Mean pulmonary artery blood pressure. f = Respiratory frequency.

Table 3—Mean ± SEM values for blood gas analyses after IV administration of xylazine in 6 horses anesthetized with isoflurane

	Pao_2 (mm Hg)		$Paco_2$ (mm Hg)	
Time	**0.5 mg/kg**	**1.0 mg/kg**	**0.5 mg/kg**	**1.0 mg/kg**
Before anesthesia	104 ± 6	98 ± 8	45.0 ± 0.6	44.5 ± 1.3
During anesthesia				
Before XYL	286 ± 80	215 ± 55	61.9 ± 3.5	68.4 ± 6.9
After XYL (Min)				
1	283 ± 69	251 ± 60	63.9 ± 6.3	61.1 ± 4.4
2	286 ± 75	241 ± 69	64.9 ± 2.4	68.7 ± 7.0
3	279 ± 69	240 ± 69	65.8 ± 4.6	66.7 ± 5.9
4	275 ± 71	257 ± 73	69.7 ± 4.3	66.8 ± 4.7
6	266 ± 70	249 ± 71	70.8 ± 6.7	71.7 ± 5.0
8	252 ± 70	235 ± 68	69.7 ± 7.9	73.7 ± 5.5
10	249 ± 66	214 ± 64	69.4 ± 6.5	74.1 ± 6.4
12	222 ± 61	193 ± 61	71.3 ± 8.8	73.8 ± 7.0
18	222 ± 53	166 ± 49	69.1 ± 6.5	69.8 ± 7.4
30	254 ± 59	175 ± 57	67.8 ± 8.2	58.5 ± 3.4
45	284 ± 77	180 ± 56	69.8 ± 11.7	64.1 ± 4.4
60	288 ± 74	186 ± 59	57.2 ± 2.1	63.9 ± 4.8
90	218 ± 78	170 ± 57	67.9 ± 8.3	61.0 ± 2.4
120	193 ± 72	202 ± 61	66.7 ± 6.9	55.5 ± 5.1
150	183 ± 74	146 ± 40	66.7 ± 6.4	63.6 ± 5.0
180	181 ± 74	130 ± 38	67.7 ± 8.9	66.3 ± 6.7
210	213 ± 85	142 ± 38	72.0 ± 9.9	64.3 ± 5.8
240	229 ± 76	160 ± 53	67.4 ± 7.0	67.2 ± 7.7

Table 4—Mean ± SEM blood glucose concentration at various times before and after administration of xylazine in 6 horses anesthetized with isoflurane

	Xylazine (mg/kg)	
Time	**0.5**	**1.0**
Before anesthesia		
1 day	95 ± 2	111 ± 5
Immediately preceding	98 ± 5	115 ± 26
During anesthesia		
Before xylazine	127 ± 5	142 ± 11
After xylazine (min)		
12	193 ± 7* (52)	204 ± 3* (44)
30	214 ± 14* (69)	271 ± 7*† (91)
60	199 ±13* (57)	267 ± 21*† (88)
120	172 ±16* (35)	218 ± 21*† (54)
240	146 ±14* (15)	167 ± 20* (18)
After anesthesia		
1 hour	145 ± 11*	155 ± 21*
1 day	114 ± 5	106 ± 10

*Within a column, values differ significantly ($P < 0.05$) from those for before xylazine during anesthesia.†Within a row, values differ significantly ($P < 0.05$) from value for 0.5 mg/kg. Values within parentheses indicate mean percentage change from values for before xylazine during anesthesia.

Urine results—Because of technical difficulties associated with 1 horse, complete data on urinary flow were collected for only 5 horses after XYL administration during anesthesia. Urine flow in these horses increased, but not significantly ($P = 0.07$), after administration of XYL (**Table 5**). During the 2 hours following XYL injection, mean urine flow was 30 and 59% (for 0.5 and 1.0 mg/kg, respectively) more than that measured during the period immediately before XYL injection.

Table 5—Mean ± SEM urine flow (ml/kg/h) measured before and after IV administration of xylazine in 5 horses anesthetized with isoflurane

		After xylazine (h)	
Xylazine (mg/kg)	**Before xylazine**	**0 to 2**	**2 to 4**
0.5	0.64 ± 0.15	0.88 ± 0.38	0.58 ± 0.22
1.0	0.92 ± 0.20	1.30 ± 0.41	0.88 ± 0.35

Values were analyzed by use of a 2-way repeated-measures ANOVA.

Discussion

Anesthetic potency (also referred to as anesthetic requirement) commonly is described as the dose of anesthetic drug that eliminates purposeful movement (or some other response in which a reduction or loss of perception is implied) in response to a noxious stimulus in 50% of the subjects. For more than 3 decades since its original description,[23,24] the MAC of an inhalation anesthetic has been regarded as the standard index of potency for that type of general anesthetic.

In previous studies, MAC for isoflurane in oxygen in horses that did not receive concurrent medications was 1.31%.[12] Mean of all control isoflurane MAC measured in the study reported here was 1.64%. We do not have reason to attribute the difference between those previous results and the results reported here for isoflurane MAC in horses to anything other than typical variability within a population.

The MAC for an inhalation anesthetic represents a single point on the dose-response curve of that anesthetic. This concept has been useful for analyzing physiologic and pharmacologic factors that may influence the state of general anesthesia. In this study, we indirectly assessed CNS depressant effects (ie, sedation, analgesia) of XYL by measuring its effect on isoflurane MAC. However, because we were interested in gaining insight into the magnitude and duration of XYL on CNS depressant effects, it was necessary to use a modified version of the technique previously used to determine MAC in horses.[12] Two special considerations

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for the modified approach were the need for steady-state or near steady-state alveolar concentration of isoflurane at the time of noxious stimulation and recognition of the lack of steady-state plasma-drug conditions associated with XYL administration (ie, the time-related decrease in plasma XYL concentration and consequent influence on MAC).

Xylazine caused a profound and significant decrease in isoflurane MAC (Table 1, Fig 1). The magnitude of effect of XYL on isoflurane MAC was dose- and time-related. It is appropriate to discount the lack of significance of the maximal response measured for each of the 2 dosages of XYL, because the timing of these measurements differed. Although difficult to compare directly, the reductions in MAC reported here are also in qualitative agreement with those determined for a single dose of XYL administered to horses anesthetized by use of halothane.[11] Relating data from the study reported here with those reported elsewhere[5] for dogs anesthetized by use of halothane suggests that the anesthetic-sparing effect of XYL is similar in horses and dogs (ie, the change in MAC is similar at approx 70 to 90 minutes after XYL administration).

In this study, the actions of XYL were not evaluated under steady-state (eg, constant IV infusion of drug) conditions. Consequently, we are unable to precisely define the peak magnitude of its effect on MAC. Studies[a] of detomidine, another commonly administered α-2 agonist, provide an example of a protocol that could be used to derive more meaningful information in this regard. Regardless, review of time-MAC reduction curves for XYL (Fig 1) suggests that XYL administration at a rate of 0.5 mg/kg will influence MAC for approximately 2 hours after IV injection and that XYL administration at a rate of 1.0 mg/kg will influence isoflurane anesthetic requirement in healthy horses for at least 3 hours after injection. In reaching these conclusions, we considered that changes in MAC of ± 10% may be within the limits of experimental noise and, therefore, discounted the clinical importance of values within this range (ie, minimal possibility of detecting that results within a range of ± 10% truly differ from an original value).

The purpose of the study reported here was not to characterize the influence of XYL on cardiovascular actions of isoflurane. However, circumstances permitted gathering of limited data on hemodynamic performance at a constant depth of anesthesia (Table 2). The data were limited in depth and breadth but represented close approximations of conditions immediately before injection of XYL and at specific times after injection (ie, time points for a constant value of isoflurane alone [before XYL] and isoflurane plus XYL [after XYL]; Fig 1). It is not appropriate to assume broad generalizations from these data, but it is interesting to review the data and to compare them with data derived from a previous investigation in which the same 2 doses of XYL were administered IV to horses anesthetized with halothane at a constant dose of 1.2 MAC.[14] It is important to remember 3 distinctions between the study reported here and that previous study. First, isoflurane was used in this study, whereas halothane was used in the previous investigation. Second, control anesthetic values differed slightly, (ie, isoflurane MAC 1.0 in this study vs halothane MAC 1.2 in the previous study). Third, the depth of anesthesia was maintained constant throughout the study reported here (ie, initially isoflurane alone and then isoflurane plus XYL, whereby isoflurane administration was adjusted over time to compensate for the time-related effect of XYL to decrease isoflurane MAC), whereas in the former study, XYL was injected into horses that were maintained at a constant background of halothane MAC 1.2 (ie, after XYL injection, anesthetic depth increased beyond MAC 1.2 and then slowly returned toward conditions that existed before XYL injection). Considering the limitations imposed by small sample size and the aforementioned 3 distinctions, analysis of these data suggests that at light planes of anesthesia, XYL has minimal influence on measures of hemodynamic performance such as heart rate and arterial blood pressure, but when added to a background of general anesthesia, XYL contributes to additional cardiovascular depression.[14] Another interesting comparison and interpretation of these data without apparent explanation at this time is that the use of XYL to maintain a constant dose of anesthesia abolishes temporal cardiovascular changes seen when general anesthesia is maintained in horses with isoflurane alone.[25]

Values for Pa_{O_2} and Pa_{CO_2} in unanesthetized horses and horses immediately before XYL injection during isoflurane-induced anesthesia were considered normal and comparable to those previously reported under similar conditions of study.[12,18] Some of the small variation in Pa_{O_2} and Pa_{CO_2} reported here after XYL injection was associated with time of blood collection and influence of manipulation in end-tidal isoflurane concentration that was performed to compensate for the time-dependent decline in XYL effect and our efforts to maintain a constant plane of general anesthesia. Regardless, Pa_{O_2} or Pa_{CO_2} did not change significantly with dosage of XYL or time after XYL administration. Lack of change in respiratory frequency and Pa_{CO_2} suggests that alveolar ventilation did not change. Lack of change in both Pa_{O_2} and Pa_{CO_2} following XYL administration is noteworthy in that it differs from information contained in 2 reports.[26,27] First, in a study in which XYL was given to horses anesthetized at a constant dose of halothane MAC 1.2, Pa_{CO_2} increased, and Pa_{O_2} decreased.[26] The fact that Pa_{CO_2} did not increase in the study reported here, in which we used a constant anesthetic depth but varying dose of XYL, but did increase in the previous study lends further support to the belief that this change was associated with an increase in anesthetic depth rather than a specific influence on direct α_2-agonist influence on chemoreceptor control of ventilation. A portion of the change in Pa_{O_2} in that other study can be explained on the basis of an increasing anesthetic-depth-related decrease in alveolar ventilation (ie, an increased Pa_{CO_2}), but there also was speculation in that study that at least part of the change was associated with a XYL-pulmonary blood flow shunt-like effect. The findings of that study support α_2-related changes in Pa_{O_2} that have been observed in ruminant species.[27] Analysis of results for the study reported here do not resolve the issues regarding effect (or lack of effect) of an α_2-agonist on

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efficiency of arterial oxygenation in horses; they only add to the controversy. Furthermore, unlike the results of another study[25] in which time-related changes in $PaCO_2$ accompanied isoflurane-induced (MAC 1.2) anesthesia, $PaCO_2$ after XYL administration did not change with time in the study reported here. This suggests a direct or indirect α_2-modifying effect on an unknown mechanism for temporal change in ventilation during isoflurane-induced anesthesia in horses.

Administration of α_2-agonists induces hyperglycemia in awake and anesthetized horses,[13,28-32] changes that, in part, are a result of a decrease in serum concentration of insulin.[28,29] Results of the study reported here (Table 4) are in qualitative agreement with previous reports of hyperglycemia. However, in comparison with closely comparable studies,[13,28,29] results from the study reported here are quantitatively distinctive. Both the absolute and relative magnitude of increase in serum glucose concentration after XYL administration in the horses reported here was noticeably increased, and the duration of this effect was increased as well. A similar effect was not detected in horses anesthetized with XYL and ketamine.[29] Blood glucose concentration increased, but not significantly, after induction of anesthesia with isoflurane but before XYL injection, compared with values for these horses before anesthesia (Table 4). Additional studies are necessary to confirm this seemingly augmented response to XYL administration during isoflurane-induced anesthesia.

Administration of α_2-drugs will transiently increase urine production in awake and anesthetized horses.[13,30-32] Despite increases in urine volume that ranged, on average, from 30 to 60% during the initial 2 hours following XYL injection, we were unable to detect significant changes. Before questioning results of previous studies, it is important to mention that results of the study reported here were limited by the number of horses in the study and scope of the study (ie, urine collected during a 2-hour period). We speculate that it is probable, assuming our results remained consistent, that a small increase in the number of horses (1 or 2 additional horses) and, in particular, an interval of 30 minutes between subsequent urine collections[13] would have provided a clear picture of XYL actions during isoflurane-induced anesthesia.

It also was of interest to compare results of an earlier study of XYL action in awake horses[13] to results from the study reported here. In both studies, XYL increased urine production from baseline values in awake or anesthetized conditions, but on the basis of this admittedly indirect comparison, it appears that, compared with awake horses, isoflurane-induced anesthesia limited urine production by 39 to 55% following XYL administration. In addition, urine production during anesthesia in the horses reported here reached values for awake (not medicated) horses only after administration of the greatest XYL dosage (1.0 mg/kg). Urine production in the previously reported study of awake unmedicated horses[13] closely mimicked results reported a few years earlier for clinically normal horses under similar environmental conditions.[33]

The extent to which urine production during anesthesia induced by use of agents that included an α_2-agonist would have improved by increasing the IV administration of fluids remains to be determined. However, analysis of our results indicated altered urine production that accompanies anesthesia and XYL administration is not trivial. Accordingly, this information should be considered, especially for clinical circumstances, in determining guidelines for IV administration of fluids for a particular horse and the need for bladder catheterization to ensure urine removal in situations in which anesthesia may be prolonged.

[a]Dunlop CI, Daunt DA, Chapman PL, et al. The anesthetic potency of 3 steady-state plasma levels of detomidine in halothane anesthetized horses (abstr), in *Proceedings*. 4th Int Congr Vet Anesth, 1991;7.

[b]Steffey EP, Pascoe PJ. Xylazine reduces the isoflurane MAC in horses (abstr). *Vet Surg* 1991;20:158.

[c]YSI Tele-thermometer Model 43, Yellow Springs Instrument Co, Yellow Springs, Ohio.

[d]Model 7 Polygraph, Grass Instruments, Quincy, Mass.

[e]Insyte, Becton-Dickinson, Sandy, Utah.

[f]Model P23D, Division of Mark IV Industries, Oxnard, Calif.

[g]LB-2 anesthetic analyzer, Sensormedics Corp, Anaheim, Calif.

[h]Primary gas standards, Matheson Gas Products, Newark, Calif.

[i]OM-11, Sensormedics Corp, Anaheim, Calif.

[j]LB-2 CO_2 analyzer, Sensormedics Corp, Anaheim, Calif.

[k]Medspec 1, PPG Biomedical Systems, Lenexa, Kan.

[l]Fleisch No. 4, Instrumentation Associates Inc, NY.

[m]ABL 330, Radiometer America, Cleveland, Ohio.

[n]Clinical Biochemistry Laboratory, Veterinary Medical Teaching Hospital, University of California, Davis, Calif.

References

1. Maze M, Birch B, Vickery RG. Clonidine reduces halothane MAC in rats. *Anesthesiology* 1987;67:868–869.

2. Segal IS, Vickery RG, Walton JK, et al. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha-2 adrenergic receptor. *Anesthesiology* 1988;69:818–823.

3. Segal IS, Vickery RG, Maze M. Dexmedetomidine decreases halothane anesthetic requirements in rats. *Acta Vet Scand* 1989;85(suppl):55–59.

4. Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha adrenergic agonist. *Anesth Analg* 1982;61:741–745.

5. Tranquilli WJ, Thurmon JC, Corbin JE, et al. Halothane-sparing effect of xylazine in dogs and subsequent reversal with tolazoline. *J Vet Pharmacol Ther* 1984;7:23–28.

6. Ewing KK, Mohammed HO, Scarlett JM, et al. Reduction of isoflurane anesthetic requirement by medetomidine and its restoration by atipamezole in dogs. *Am J Vet Res* 1993;54:294–299.

7. Devcic A, Schmeling WT, Kampine JP, et al. Oral dexmedetomidine preserves baroreceptor function and decreases anesthetic requirements of halothane-anesthetized dogs. *Anesthesiology* 1994;81:419–430.

8. Kaukinen S, Pyykko K. The potentiation of halothane anaesthesia by clonidine. *Acta Anaesthesiol Scand* 1979;23:107–111.

9. Buhrer M, Mappes A, Lauber R, et al. Dexmedetomidine decreases thiopental dose requirement and alters distribution pharmacokinetics. *Anesthesiology* 1994;80:1216–1227.

10. Aantaa R, Jaakola M-L, Kallio A, et al. Reduction of the minimum alveolar concentration of isoflurane by dexmedetomidine. *Anesthesiology* 1997;86:1055–1060.

11. Muir WW III, Wagner AE, Hinchcliff KW. Cardiorespiratory and MAC-reducing effects of α_2-adrenoreceptor agonists in horses. In: Short CE, Vanpoznak A, eds. *Animal pain*. 1st ed. New York: Churchill Livingstone Inc, 1992;201–212.

12. Steffey EP, Howland D Jr, Giri S, et al. Enflurane, halothane and isoflurane potency in horses. *Am J Vet Res* 1977;38:1037–1039.

13. Thurmon JC, Steffey EP, Zinkl JG, et al. Xylazine causes

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transient dose-related hyperglycemia and increased urine volumes in mares. *Am J Vet Res* 1984;45:224–227.

14. Steffey EP, Kelly AB, Farver TB, et al. Cardiovascular and respiratory effects of acetylpromazine and xylazine on halothane-anesthetized horses. *J Vet Pharmacol Ther* 1985;8:290–302.

15. Steffey EP, Howland D Jr. Comparison of circulatory and respiratory effects of isoflurane and halothane anesthesia in horses. *Am J Vet Res* 1980;40:821–825.

16. Ozanne GM, Young WG, Mazzei WJ, et al. Multipatient anesthetic mass spectrometry: rapid analysis of data stored in long catheters. *Anesthesiology* 1981;55:62–70.

17. Steffey EP, Woliner MJ, Young WG, et al. Two years' experience with a multi-station, multi-anesthetic and respiratory gas analysis system (MARGAS). In: Hall LW, ed. *Proceedings of the 4th International Congress of Veterinary Anaesthesia: a special supplement of the Journal of Veterinary Anaesthesia*. Cambridge: Association of Veterinary Anaesthetists, 1991;83–85.

18. Steffey EP, Dunlop CI, Farver TB, et al. Cardiovascular and respiratory measurements in awake and isoflurane-anesthetized horses. *Am J Vet Res* 1987;48:7–12.

19. Steffey EP, Howland D Jr. Potency of halothane-N2O in the horse. *Am J Vet Res* 1978;39:1141–1146.

20. Steffey EP, Martucci R, Howland D, et al. Meperidine-halothane interaction in dogs. *Can Anaesth Soc J* 1977;24:459–467.

21. Steffey EP, Eisele JH, Baggot JD, et al. Influence of inhaled anesthetics on the pharmacokinetics and pharmacodynamics of morphine. *Anesth Analg* 1993;77:346–351.

22. Steffey EP, Baggot JD, Eisele JH, et al. Morphine-isoflurane interaction in dogs, swine and rhesus monkeys. *J Vet Pharmacol Ther* 1994;17:202–210.

23. Merkel G, Eger EI II. A comparative study of halothane and halopropane anesthesia including method for determining equipotency. *Anesthesiology* 1963;24:346–357.

24. Eger EI II, Saidman LJ, Brandstater B. Minimal alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* 1965;26:756–763.

25. Steffey EP, Hodgson DS, Dunlop CI, et al. Cardiopulmonary function during 5 hours of constant-dose isoflurane in laterally recumbent, spontaneously breathing horses. *J Vet Pharmacol Ther* 1987;10:290–297.

26. Bailey PL, Sperry RJ, Johnson GK, et al. Respiratory effects of clonidine alone and combined with morphine in humans. *Anesthesiology* 1991;74:43–48.

27. Eisenach JC. Intravenous clonidine produces hypoxemia by a peripheral alpha-2 adrenergic mechanism. *J Pharmacol Exp Ther* 1988;244:247–252.

28. Thurmon JC, Neff-Davis CA, Davis LE, et al. Xylazine hydrochloride-induced hyperglycemia and hypoinsulinemia in thoroughbred horses. *J Vet Pharmacol Ther* 1982;5:241–245.

29. Tranquilli WJ, Thurmon JC, Neff-Davis CA, et al. Hyperglycemia and hypoinsulinemia during xylazine-ketamine anesthesia in thoroughbred horses. *Am J Vet Res* 1984;45:11–14.

30. Gasthuys F, van den Hende C, de Moor A. Study of some ionary parameters in horse serum and urine during halothane anaesthesia with xylazine premedication. *Zentralbl Veterinarmed A* 1986;33:791–800.

31. Gasthuys F, Terpstra P, van den Hende C, et al. Hyperglycaemia and diuresis during sedation with detomidine in the horse. *Zentralbl Veterinarmed A* 1987;34:641–648.

32. Gasthuys F, van den Hende C, de Moor A. Biochemical changes in blood and urine during halothane anaesthesia with detomidine premedication in the horse. *Zentralbl Veterinarmed [A]* 1988;35:655–664.

33. Rumbaugh GE, Carlson GP, Harrold D. Urinary production in the healthy horse and in horses deprived of feed and water. *Am J Vet Res* 1982;43:735–737.

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