Effects of α_2-adrenergic receptor agonists on urine production in horses deprived of food and water

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Objective—To quantitate the dose- and time-related effects of IV administration of xylazine and detomidine on urine characteristics in horses deprived of feed and water.

Animals—6 horses.

Procedure—Feed and water were withheld for 24 hours followed by IV administration of saline (0.9% NaCl) solution, xylazine (0.5 or 1.0 mg/kg), or detomidine (0.03 mg/kg). Horses were treated 4 times, each time with a different protocol. Following treatment, urine and blood samples were obtained at 15, 30, 60, 120, and 180 minutes. Blood samples were analyzed for PCV and serum concentrations of total plasma solids, sodium, and potassium. Urine samples were analyzed for pH and concentrations of glucose, proteins, sodium, and potassium.

Results—Baseline (before treatment) urine flow was 0.30 ± 0.03 mL/kg/h and did not significantly change after treatment with saline solution and low-dose xylazine but transiently increased by 1 hour after treatment with high-dose xylazine or detomidine. Total urine output at 2 hours following treatment was 312 ± 101 mL versus 4,845 ± 272 mL for saline solution and detomidine, respectively. Absolute values of urine concentrations of sodium and potassium also variably increased following xylazine and detomidine administration.

Conclusions and Clinical Relevance—Xylazine and detomidine administration in horses deprived of feed and water causes transient increases in urine volume and loss of sodium and potassium. Increase in urine flow is directly related to dose and type of α_2-adrenergic receptor agonist. Dehydration in horses may be exacerbated by concurrent administration of α_2-adrenergic receptor agonists. (*Am J Vet Res* 2004;65:1342–1346)

Dehydration commonly accompanies a variety of unhealthy conditions in horses that are in need of veterinary care. It has many causes but is fundamentally the result of inadequate water intake during periods of normal or excessive fluid losses. Urinary fluid loss and other physiologic alterations have been described for healthy horses and horses deprived of feed and water.[1-4]

Horses are commonly treated with an α_2-adrenergic receptor agonist such as xylazine or detomidine for sedation and analgesia. These drugs are known to transiently increase urinary output in awake[5-7] and anesthetized[8,9] healthy equids. We hypothesized that these drugs will override normal physiologic compensation for an existing fluid deficit in horses and, in the absence of intervention, exacerbate existing hydration conditions. The purpose of the study reported here was to characterize urinary output in horses deprived of food and water for 24 hours and then given xylazine or detomidine.

Materials and Methods

Animals—Six healthy unmedicated female horses that ranged from 5 to 22 years of age (mean [± SE], 12.5 ± 3.3 years of age) and weighed 471 ± 23 kg were included in this study. The Animal Use and Care Committee of the Faculty of Veterinary Science of the National Autonomous University of México approved the study protocol.

Each horse was treated 4 times, each time with a different drug treatment protocol that was randomly assigned a priori. A minimum of 7 days was provided between drug treatment protocols for each horse. Studies were always conducted in the morning during the spring months in Mexico City. Mean temperature and relative humidity were 18°C and 52%, respectively. Feed and water were withheld 24 hours before each drug treatment protocol. A day before each treatment, horses were determined to be healthy on the basis of physical examination findings, CBC determination, and urinalysis results.

The morning following withholding of food and water, horses were prepared for urine and blood sample collection. A catheter was percutaneously inserted into the jugular vein by use of an aseptic technique and a valve attached. This IV route was used for blood sample collection and drug administration. The tail was wrapped with gauze. The vulva and perineal region were cleansed with antiseptic soap and water. The urinary bladder was then catheterized via sterile-gloved hands and a 30-F Foley style urinary catheter. The 30-mL balloon of the catheter was filled with sterile saline (0.9% NaCl) solution to anchor it within the bladder. The urinary bladder was emptied by use of suction and the air displacement technique. After the bladder was emptied, the catheter was connected to an extension tube and a closed-system urine collector. Urine was then collected passively by gravity and, at appropriate times, an empty bladder was corroborated by use of suction and the air displacement technique. Urine volume was then measured by use of a calibrated volumetric cylinder.

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Study conditions—Urine was collected for 2 hours, and a composite urine sample along with a sample of jugular venous blood were used for determination of baseline values. Shortly after emptying the bladder, 1 of 4 treatments was administered to the horse as follows: xylazine hydrochloride (0.5 or 1.0 mg/kg, 5 mL, IV), detomidine hydrochloride (0.03 mg/kg, 5 mL, IV), or saline solution (5 mL, IV). We considered an IV administration of 1.0 mg of xylazine/kg and 0.03 mg of detomidine/kg closely equivalent doses with regard to sedative and analgesic effects.[9] Urine and blood samples were then obtained during the next 2 hours according to the following schedule: 15, 30, 60, and 120 minutes. Sample collection continued for an additional hour if horses cooperated as drug-related sedative effects waned. Blood was analyzed for PCV, **total plasma solids (TP)** concentration (by refractometry), and **serum sodium (Na_S)** and **serum potassium (K_S)** concentrations (by photometry). Samples of well-mixed and timed amounts of urine were refrigerated until they were processed in the laboratory within 2 hours of the conclusion of each drug treatment protocol. Urine samples were analyzed for pH, glucose concentration, and proteins by use of a qualitative enzyme test.[a] Also, **urine sodium (Na_U)** and **potassium (K_U)** concentrations were determined by use of photometry, and urine specific gravity was determined by use of refractometry. Immediately following each drug treatment protocol, horses were returned to normal conditions in terms of food and water availability.

Statistical analysis—Values are expressed as means (± SE) unless indicated differently. Inferential analysis was performed by use of a 2-way repeated measures ANOVA (with factors of treatment and time) and an associated post hoc Dunnett test (multiple comparisons vs baseline). A value of $P < 0.05$ was considered significant.

Results

Results of CBC determination and urinalysis for horses before the initiation of each drug treatment protocol were within reference range limits. Following xylazine and detomidine administration, horses had typical α_2-adrenergic receptor agonist-induced sedated behavior for approximately 2 hours. Beyond 2 hours after drug injection, sedative effects were, not surprisingly, variable, and as a result, behavior of some horses made it difficult to maintain adequate urine sample collection conditions. Accordingly, the number of observations after 2 hours of treatment was variable (by this point, horses had been restrained in stocks and catheterized before and after treatment observations for approx 5 hours). As a result, inferential statistics were not computed on results from the third hour after treatment for any drug treatment protocol.

No significant difference was found in baseline (predrug) urine flow among horses preceding the 4 drug treatment protocols. The combined baseline urine flow (ie, 4 baseline periods for each of 6 horses) was

Table 1—Mean (± SE) urine values before (time 0, baseline) and after IV injection of saline (0.9% NaCl) solution, xylazine, or detomidine in 6 healthy horses deprived of food and water for 24 hours.

		Time (min)					
Variables	**Treatments (IV)**	**0**	**15**	**30**	**60**	**120**	**180**
Flow (mL/h/kg)	Saline	131 ± 23	51 ± 14	27 ± 9	68 ± 12 (146 ± 17)	167 ± 91	201 ± 51
	0.5 XYL	125 ± 26	163 ± 157	53 ± 76	280 ± 136 (497 ± 220)	336 ± 151	110 ± 1 (n = 2)
	1.0 XYL	207 ± 28	29 ± 16	228 ± 148	775 ± 293 (1,031 ± 380)*	548 ± 177	287 ± 63 (5)
	0.03 DET	101 ± 14	7 ± 1	26 ± 10	1,012 ± 318 (1,044 ± 324)*	3,801 ± 250*	1080 ± 236 (3)
Specific gravity	Saline	1.032 ± 0.002	1.034 ± 0.003	1.034 ± 0.002	1.032 ± 0.002	1.034 ± 0.004	1.030 ± 0.004 (4)
	0.5 XYL	1.030 ± 0.002	1.030 ± 0.002	1.029 ± 0.002	1.021 ± 0.006*	1.023 ± 0.006	1.041 ± 0.003 (2)
	1.0 XYL	1.028 ± 0.003	1.030 ± 0.003	1.018 ± 0.005*	1.016 ± 0.005*	1.016 ± 0.005*	1.019 ± 0.013 (5)
	0.03 DET	1.036 ± 0.002	1.036 ± 0.002	1.032 ± 0.004	1.010 ± 0.002*	1.005 ± 0.001*	1.013 ± 0.002 (3)
Na (mEq/L)	Saline	167 ± 18	142 ± 11	149 ± 10	136 ± 12	145 ± 17	154 ± 12 (4)
	0.5 XYL	183 ± 35	163 ± 32	164 ± 28	158 ± 28	143 ± 24	85 ± 25 (2)
	1.0 XYL	148 ± 38	142 ± 42	130 ± 57	146 ± 43	169 ± 40	163 ± 47 (5)
	0.03 DET	212 ± 30	208 ± 35	175 ± 23	118 ± 33*	111 ± 29*	175 ± 14 (3)
K (mEq/L)	Saline	185 ± 38	196 ± 34	189 ± 32	203 ± 32	179 ± 28	177 ± 32 (4)
	0.5 XYL	170 ± 22	186 ± 24	166 ± 25	90 ± 28*	109 ± 30*	177 ± 45 (2)
	1.0 XYL	129 ± 23	152 ± 27	59 ± 29*	61 ± 23*	77 ± 27*	87 ± 6 (5)
	0.03 DET	171 ± 25	172 ± 19	142 ± 33	31 ± 14*	28 ± 20*	17 ± 7 (3)

Values in parentheses for urine flow at 60 minutes indicate the total urine output (mL) for the first hour of treatment.
*Significantly ($P < 0.05$) different from baseline values.
0.5 XYL = Xylazine (0.5 mg/kg). 1.0 XYL = Xylazine (1.0 mg/kg). 0.03 DET = Detomidine (0.03 mg/kg).

0.301 ± 0.031 mL/kg/h (median, 0.277 mL/kg/h; range, 0.018 to 0.777 mL/kg/h). Urine flow was recorded following the 4 drug treatment protocols for all time points (**Table 1**). Urine flows were normalized on the basis of body mass (in kg) on an hourly basis for 3 hours after treatment (**Figure 1**). Urine output for the first hour was derived by adding the values for the 0- to 15-, 15- to 30-, and 30- to 60-minute sample collection times. Urine flow was similarly and significantly increased by the end of the first hour following treatment with detomidine or high-dose xylazine, compared with baseline values. After the first hour, urine flow decreased in horses treated with high-dose xylazine and seemed to return to before drug treatment values by 3 hours after treatment (n = 5), whereas urine flow of horses at 2 hours after detomidine administration was more than 3 times the amount measured at 1 hour after detomidine administration. In 3 of 6 horses from which data were obtained, urine flow was still notably increased at 3 hours after detomidine treatment. Total urine output for horses at 2 hours following treatment was 312 ± 101 mL, 832 ± 275 mL, 1,580 ± 538 mL, and 4,845 ± 272 mL for saline solution, low-dose and high-dose xylazine, and detomidine, respectively. This represents increases of approximately 2.7, 5, and 15 times basal urine flow following low-dose and high-dose xylazine and detomidine administration, respectively.

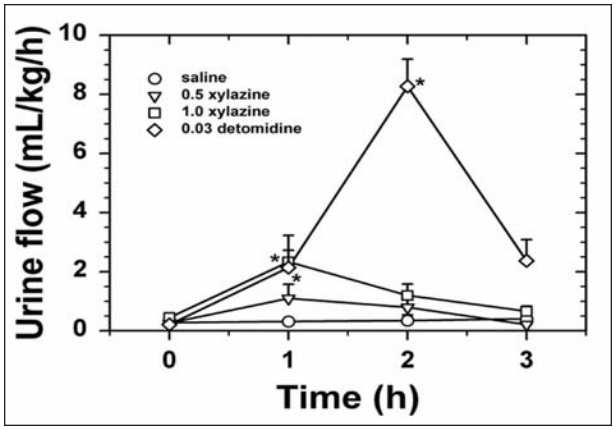

Figure 1—Urine flow versus time before (0 hour, baseline) and after treatment with saline (0.9% NaCl) solution, xylazine (0.5 and 1.0 mg/kg), or detomidine (0.03 mg/kg) in 6 horses. At 3 hours, n = 4, 2, 3, and 5 for detomidine, high-dose and low-dose xylazine, and saline solution-treated horses, respectively. *Significantly ($P < 0.05$) different from baseline values.

The baseline values for urine specific gravity; PCV; and concentrations of Na_U, Na_S, K_U, K_S, and TP were within reference range limits (Tables 1 and 2). Accompanying the time and drug-related increases in urine flow were decreases from baseline values in urine specific gravity (following xylazine and detomidine administration), Na_U concentration (following detomi-

Table 2—Mean (± SE) blood values before (time 0, baseline) and after IV injection of saline solution, xylazine, or detomidine in 6 healthy horses deprived of food and water for 24 hours.

		Time (min)					
Variables	**Treatments (IV)**	**0**	**15**	**30**	**60**	**120**	**180**
PCV (%)	Saline	36.0 ± 1.7	35.5 ± 1.8	36.7 ± 2.1	37.0 ± 1.9	38.0 ± 2.8	35.8 ± 1.5 (n = 4)
	0.5 XYL	38.3 ± 1.7	34.3 ± 0.8*	32.3 ± 0.8*	35.0 ± 1.2*	41.8 ± 1.9*	48.5 ± 1.5 (2)
	1.0 XYL	40.7 ± 3.0	35.7 ± 2.0*	33.2 ± 1.5*	31.0 ± 1.6*	36.7 ± 2.2*	40.4 ± 2.6 (5)
	0.03 DET	35.8 ± 1.1	40.0 ± 2.0*	39.7 ± 1.9*	35.5 ± 1.4	30.0 ± 1.5*	34.3 ± 3.0 (3)
TP (g/dL)	Saline	7.02 ± 0.28	6.97 ± 0.29	7.08 ± 0.32	7.22 ± 0.33	7.28 ± 0.30	6.93 ± 0.21 (4)
	0.5 XYL	6.92 ± 0.29	6.75 ± 0.21	6.70 ± 0.23	6.68 ± 0.12	7.40 ± 0.26*	7.40 ± 0.20 (2)
	1.0 XYL	6.80 ± 0.23	6.70 ± 0.20	6.70 ± 0.16	6.52 ± 0.23	7.07 ± 0.32	6.96 ± 0.13 (5)
	0.03 DET	6.68 ± 0.18	7.08 ± 0.31	6.87 ± 0.14	6.78 ± 0.21	6.65 ± 0.22	6.60 ± 0.20 (3)
Na (mEq/L)	Saline	140 ± 1	138 ± 2	140 ± 1	140 ± 1	140 ± 2	140 ± 2 (4)
	0.5 XYL	141 ± 1	140 ± 1	139 ± 1	140 ± 1	140 ± 1	147 ± 1 (2)
	1.0 XYL	141 ± 1	141 ± 1	141 ± 1	141 ± 1	142 ± 1	143 ± 1 (5)
	0.03 DET	141 ± 1	141 ± 1	140 ± 1	141 ± 1	142 ± 1	145 ± 1 (3)
K (mEq/L)	Saline	3.83 ± 0.06	3.69 ± 0.06	3.71 ± 0.06	3.79 ± 0.11	3.64 ± 0.11	3.68 ± 0.10 (4)
	0.5 XYL	3.85 ± 0.08	3.58 ± 0.13	3.80 ± 0.17	3.83 ± 0.14	3.74 ± 0.13	3.31 ± 0.46 (2)
	1.0 XYL	4.22 ± 0.33	3.64 ± 0.03	3.72 ± 0.06	3.78 ± 0.05	3.69 ± 0.06	3.64 ± 0.11 (5)
	0.03 DET	3.69 ± 0.07	3.70 ± 0.07	3.75 ± 0.10	3.84 ± 0.09	3.76 ± 0.09	3.70 ± 0.03 (3)

See Table 1 for key.

dine administration), and K_U concentration (following xylazine and detomidine administration). However, absolute amounts of Na_U and K_U increased. The TP, Na_S, and K_S concentrations did not change. The PCV also did not change following saline solution administration but decreased transiently following xylazine administration. Following detomidine administration, PCV initially increased and then decreased at 120 minutes after injection before returning to baseline. Urine pH did not change and protein was not detected in urine samples over the course of study. Small amounts of glucose were detected by dipstick testing in only 3 of the 6 horses and only following xylazine administration (detected at 30 and 180 minutes, 60 and 120 minutes, and 120 minutes for the 3 horses, respectively). No lasting effects of food and water deprivation were observed beyond the study period for any of the horses.

Discussion

In healthy unsedated horses with no restrictions to feed and water, normal urine flows of 1.24,[3] 1.12,[5] 0.52,[10] and 0.92 mL/kg/h[11] have been reported. Administration of xylazine to healthy horses[5] and ponies[7] not deprived of food and water transiently increases urine volume in a dose-related manner. For example, in 1 study,[5] IV administration of xylazine at 1.0 mg/kg to 9 otherwise unmedicated horses nearly tripled urine flow over a 2-hour period (ie, to 2.9 mL/kg/h).

Urine production in healthy horses deprived of feed and water is decreased. In horses held without feed and water for 24 hours, mean (± SD) decrease in urine production was previously reported as 0.55 ± 0.19 mL/kg/h.[3] In our study, we subjected horses to similar conditions as this previous report and found a similarly decreased urine output of 0.301 ± 0.031 mL/kg/h. Interestingly, in another study[6] in which 4 horses had feed withheld for 24 hours but water was withheld for only 12 hours, urine production was near normal with values of approximately 0.96 mL/kg/h.

In our study, we were interested in whether commonly used α_2-adrenergic receptor agonists retain their effectiveness in promoting urine flow in horses deprived of feed and water for a prolonged period that were presumed to be in a state of mild to moderate dehydration.[2,3] If these agents continue to promote increased urine flow in dehydrated horses, this information is clinically important for making treatment decisions. In support of our prediction, we found a significant transient increase in urine flow following xylazine (high dose) and detomidine administration (Figure 1). Although different in the magnitude of urine flow, our findings were qualitatively similar to results of studies of xylazine administration in clinically normal horses not deprived of food and water[5] and in horses given detomidine after withholding food and water for 12 hours.[6]

Comparing our data to previously reported results also provides indirect evidence that although α_2-adrenergic receptor agonists retain their ability to increase urine output in at least some dehydrated horses, their effectiveness in this regard is decreased. Comparison of our results following IV administration of xylazine at 0.5 and 1.0 mg/kg to earlier reported results of Thurmon et al[5] (following a similar drug treatment protocol in horses not deprived of food and water) revealed that urine flow in our horses was only approximately 60% (62% and 59% following IV administration of xylazine at 0.5 and 1.0 mg/kg, respectively) of total hourly urine flow measured in their study.[5]

Results of our study indicate that xylazine and detomidine administration (and likely other α_2-adrenergic receptor agonists) increases urine flow in hydrated and dehydrated horses. The additional drug-induced water loss from a dehydrated horse must be considered in fluid replacement plans associated with overall health care delivery.

Concentrations of Na_S and K_S did not significantly change during our study with any treatment. These findings are in agreement with those of Carlson et al[2] in unmedicated healthy horses deprived of food and water for 24 hours and of other studies of healthy horses[5] and ponies[7] given xylazine. Presumably, the lack of change in serum concentrations of these electrolytes and TP relates to the ability of horses to compensate for a short period (24 hours) of water deprivation in our study and the study by Carlson et al,[2] compared with, for example, results of the study by Tasker[10] in which an increase in serum concentration of TP and a decrease in concentration of K_S were observed following more prolonged periods of withholding food and water. In our study, except for a slightly greater PCV in horses prior to IV administration of high-dose xylazine (likely caused by random arousal behavior in some of the horses during their preparation), baseline PCV was not significantly different among horses for any of the drug treatment protocols and did not vary with time following saline solution treatment. Following xylazine administration, PCV transiently decreased, likely as a result of the sedative effect of xylazine predominating, and then increased as the sedative effects dissipated and the calm behavior was replaced by an increasingly more aroused or anxious behavior. The accompanying increased sympathetic activity would be expected to cause splenic contraction and an increased PCV. Much like the findings of Gasthuys et al[6] in horses not deprived of food and water, we found that following administration of detomidine, PCV initially increased in, then decreased in a manner similar in magnitude to that following xylazine administration. We presume this relates to initial direct sympathetic stimulating properties of detomidine and the associated splenic RBC contribution to the systemic circulation, followed in time by lessening of sympathetic tone and reversal of the earlier actions.

Our values for urine specific gravity and concentrations of Na_U, and K_U prior to drug treatment compare favorably with results of Rumbaugh et al[3] from horses deprived of food and water for 24 hours and did not significantly change in our horses following saline solution treatment. Predictably, specific gravity decreased following xylazine and detomidine administration, and the changes accompanied the time-related increases in urine flow. After drug treatment, concentrations of Na_U (following detomidine administration)

and K_U (following xylazine and detomidine administration) decreased; however, total excretion (compared with baseline values) of these electrolytes increased over the course of observation, despite withholding of food and water.

Glucosuria was detected in 3 of the horses of our study but only after detomidine administration. Hyperglycemia is a known common response to α_2-adrenergic receptor agonist administration.[5-7,11] Glucosuria in clinically normal horses results when the magnitude of serum concentrations of glucose exceeds the renal tubular maximum for reabsorption. Results of our study indicate that the magnitude of serum glucose concentration following detomidine administration reached such values.

[a]Multistix, Bayer de México, Ecatepec, Estado de México.

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