Comparison of the diuretic effects of medetomidine hydrochloride and xylazine hydrochloride in healthy cats

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Objective—To investigate dose-related diuretic effects of medetomidine hydrochloride and xylazine hydrochloride in healthy cats.

Animals—5 sexually intact cats (4 males and 1 female).

Procedures—The 5 cats received each of 11 treatments. Cats were treated by IM administration of saline (0.9% NaCl) solution (control treatment), medetomidine hydrochloride (20, 40, 80, 160, and 320 μg/kg), and xylazine hydrochloride (0.5, 1, 2, 4, and 8 mg/kg). Urine and blood samples were collected 9 times during a 24-hour period. Variables measured were urine volume, pH, and specific gravity; plasma arginine vasopressin (AVP) concentration; and creatinine and electrolyte concentrations as well as osmolality in both urine and plasma.

Results—Both medetomidine and xylazine increased urine production for up to 5 hours after injection. Xylazine had a dose-dependent diuretic effect, but medetomidine did not. Urine specific gravity and osmolality decreased in a dose-dependent manner for both drugs. Free-water clearance increased for up to 5 hours after injection, whereas glomerular filtration rate, osmolar clearance, plasma osmolality, and electrolyte concentrations did not change significantly. Area under the curve for AVP concentrations decreased in a dose-dependent manner for medetomidine but not for xylazine; however, this was not related to diuresis.

Conclusions and Clinical Relevance—Both medetomidine and xylazine induced profound diuresis in cats by decreasing reabsorption of water in the kidneys. The diuretic effect of medetomidine, including the change in AVP concentration, differed from that of xylazine. Care must be used when administering these drugs to cats with urinary tract obstruction, hypovolemia, or dehydration. (*Am J Vet Res* 2012;73:1871–1880)

The α_2-adrenoceptor agonists medetomidine and xylazine are used in veterinary medicine to induce reliable and dose-dependent sedation, analgesia, and muscle relaxation.[1] Although both drugs are used similarly in practice, there are differences between the 2 drugs. Medetomidine is a more potent, selective, and specific α_2-adrenoceptor agonist than is xylazine. The ratio of α_2-adrenoceptor selectivity to α_1-adrenoceptor selectivity of medetomidine (1,620:1) is approximately 10-fold as great as that of xylazine (160:1).[2] In addition, in contrast to xylazine, medetomidine contains an imidazole ring that has an affinity for imidazoline receptors.[3]

The α_2-adrenoceptor agonists can induce profound diuresis in several species. It has been suggested that several factors are involved in the mechanism of this diuresis. These factors include inhibition of plasma AVP secretion from the pituitary gland,[4,5] inhibition of the ability of AVP-induced cAMP formation in the kidneys,[6] redistribution of the aquaporin-2 water channel independent of changes in vasopressin activity,[7] inhibition of renin release mediated directly by specific renal α_2–adrenoceptors in the kidneys,[8] increase in plasma atrial natriuretic peptide concentrations,[9] inhibition of renal sympathetic activity,[10] osmotic diuresis attributable to hyperglycemia and glucosuria as a result of the inhibition of insulin release,[11] and inhibition of tubular sodium reabsorption.[12] However, the exact mechanism of the diuretic effect of α_2-adrenoceptor agonists is still unknown. Moreover, this mechanism may differ depending on the particular animal species.[6]

In another study recently conducted by our laboratory group,[13] we reported that the dose-dependent diuretic response to xylazine was more profound

Abbreviations	
AUC	Area under the curve
AVP	Arginine vasopressin
GFR	Glomerular filtration rate

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than that to medetomidine in healthy dogs and that medetomidine decreased plasma AVP concentrations significantly, whereas xylazine did not significantly alter plasma AVP concentrations. Furthermore, the α_2-adrenoceptor antagonists atipamezole and yohimbine antagonize diuresis induced by medetomidine and xylazine without causing meaningful hormonal changes in dogs.[14,15] Given this effect, medetomidine should be used with discretion in hypovolemic or dehydrated dogs and avoided in those with urinary tract obstruction.[16] Also, the increase in urine flow must be considered when making decisions regarding anesthetic management.[17]

To our knowledge, there are no published reports on the diuretic effects of medetomidine and xylazine in cats. Given the differences among species, it is important to examine diuretic effects of both drugs in cats. The purpose of the study reported here was to investigate the effects of both drugs on diuretic and hormonal variables in healthy cats.

Materials and Methods

Animals—Five healthy adult mixed-breed cats (4 sexually intact males and 1 sexually intact female) that had a body weight ranging from 2.9 to 5.3 kg were used in the study. They were fed a standard commercial dry food formulated for cats and raised in a laboratory with appropriate animal management facilities. Examinations performed prior to the experiments revealed that all cats were healthy, with physical examination, hematologic, and urinary values within respective reference limits. The study protocol was approved by the Animal Research Committee of Tottori University.

Experimental procedures—The 5 cats were assigned to receive each of the 11 treatments in a modified randomized design, as described elsewhere.[18] Each cat received saline (0.9% NaCl) solution (2.0 mL, IM [control treatment]), medetomidine hydrochloride (20, 40, 80, 160, or 320 µg/kg, IM), or xylazine hydrochloride (0.5, 1, 2, 4, or 8 mg/kg, IM). There was at least 1 week between successive treatments for each cat.

Food and water were withheld for 12 hours before the start of each experiment. After samples were collected at 6 hours after injection, food and water were provided. Food was then withheld again from the cats for 12 hours prior to collection of samples at 24 hours after injection. The experiments were performed in a room with the air temperature maintained at 25°C.

Sample collection—On the day before treatment administration, all cats were anesthetized with propofol, as described elsewhere.[19] A 17-gauge central venous catheter was introduced into a jugular vein of each cat. A 4F polyvinyl chloride catheter and 6F silicon balloon catheter were placed in the urinary bladder of male and female cats, respectively. Each cat was then placed in a separate cage, and a maintenance dose of Ringer's solution was administered IV for 10 hours to ensure sufficient urine production during the experiment. One hour before the start of each experiment, the bladder of each cat was emptied in preparation for subsequent collection of urine samples. Urine and blood samples were collected 9 times (before injection of the treatment [time 0; baseline] and 0.5, 1, 2, 3, 4, 5, 6, and 24 hours after injection) from each cat. After collection of samples at 6 hours, each cat again received an infusion of Ringer's solution for 10 hours, similar to that administered before the experiment.

Blood samples (2.5 mL) and urine samples were collected from the central venous and urinary catheters, respectively. An aliquot (2.0 mL) of each blood sample was mixed with EDTA for measurement of AVP concentrations, and the remaining 0.5 mL was mixed with heparin for other measurements. Blood samples were immediately centrifuged at 2,000 × *g* at 4°C for 15 minutes, and the plasma was separated and stored at −80°C until analysis. Urine samples were centrifuged at 2,000 × *g* for 5 minutes, and the supernatant was then collected and stored at −40°C until analysis.

Monitoring of behavior and physical variables—Behavioral responses were observed and physical variables, including heart rate, respiratory rate, and rectal temperature, were measured simultaneously with collection of blood and urine samples. For both medetomidine and xylazine treatments, all cats were sedated and positioned in lateral or sternal recumbency, and behaviors were recorded.

Analytic methods—Urine volume, specific gravity, and pH; urine and plasma creatinine concentrations, osmolality, and electrolyte (sodium, potassium, and chloride) concentrations; and plasma AVP concentrations were measured via procedures described elsewhere.[13] The osmolar clearance was calculated as follows: (urine osmolality × urine volume)/plasma osmolality. Free-water clearance was calculated as follows: urine volume – osmolar clearance. The GFR was assessed via creatinine clearance and calculated as follows: (urine creatinine concentration × urine volume)/plasma creatinine concentration. The fractional clearance of electrolytes was calculated as follows: (urine electrolyte concentration/plasma electrolyte concentration) × (plasma creatinine concentration/urine creatinine concentration) × 100.

Data evaluation—Statistical analysis was performed with commercially available statistical programs.[a,b] A 1-way ANOVA was used to examine the time effect within each treatment and the treatment effect at each time point. When a significant difference was detected, the Tukey test was used to compare the means. The AUC was measured by calculating the sum of the trapezoids formed by the data points. The total urine volume and the AUC of plasma AVP concentration were plotted against the doses of medetomidine or xylazine, and simple linear regression analysis was applied. When a significant difference was detected, the effect of the drug was considered to be dose related. Results were expressed as mean ± SE. For all tests, values of $P < 0.05$ were considered significant.

Results

Behavior and physical variables—The durations of sternal and lateral recumbency were prolonged in a dose-dependent manner. Abnormal behaviors, such as anxiety, muscle rigidity, or excitation-like movement,

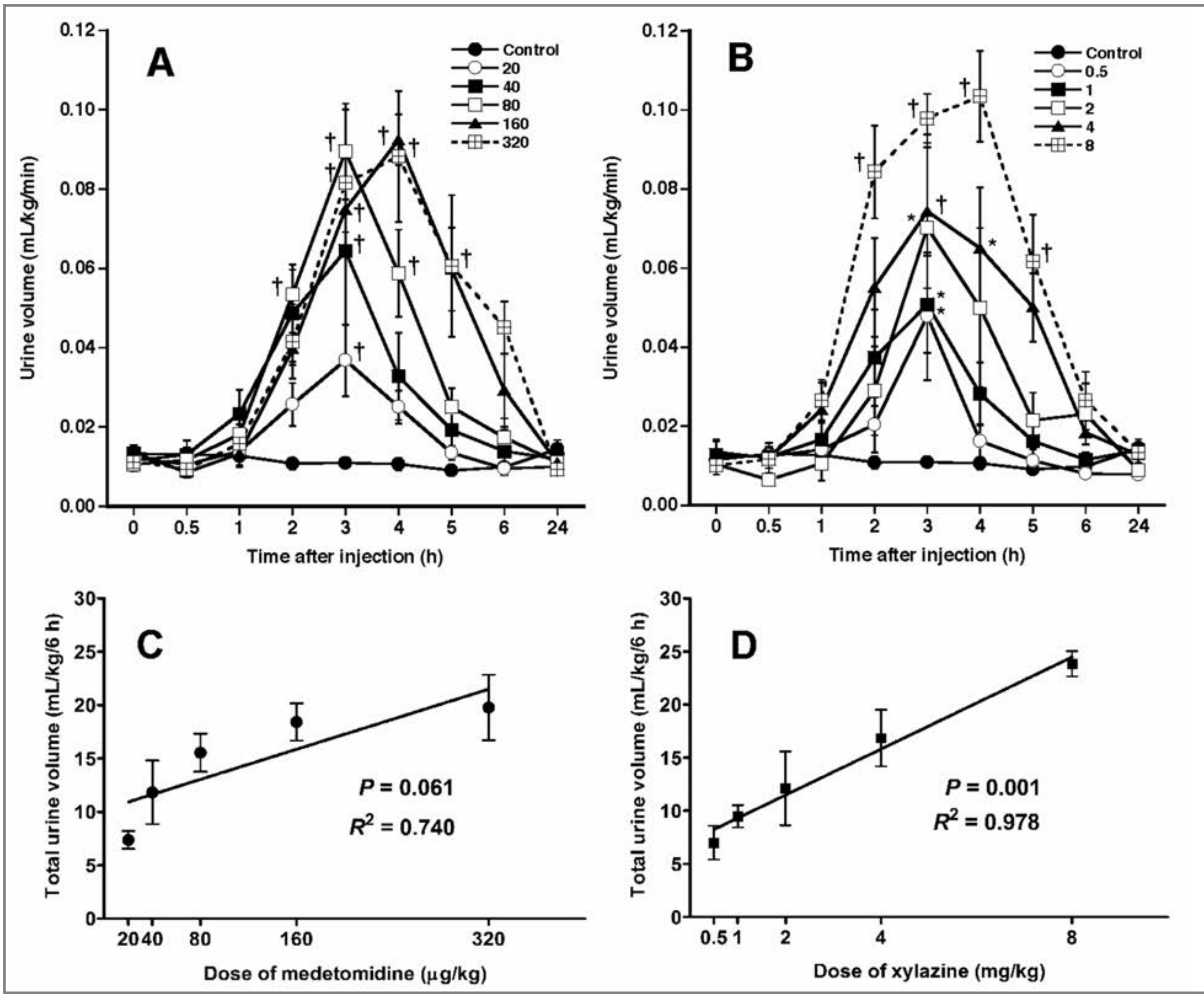

Figure 1—Mean ± SE urine volume for 5 cats after injection of saline (0.5% NaCl) solution (control treatment) or various doses of medetomidine hydrochloride (µg/kg; A) or xylazine hydrochloride (mg/kg; B) and linear regression of the total urine volume after injection of the various doses of medetomidine (C) or xylazine (D). Time of injection was designated as time 0 (baseline). *†Value differs significantly (*$P < 0.05$; †$P = 0.01$) from the baseline value.

were not observed, even with the highest doses of both drugs. Vomiting or signs of nausea were observed in all cats for both treatments. Heart rate, respiratory rate, and rectal temperature decreased in a dose-dependent manner for both medetomidine and xylazine. The lowest mean ± SE heart rate for the medetomidine and xylazine treatments was 72.4 ± 3.5 beats/min at 2 hours for 320 µg of medetomidine/kg and 81.6 ± 4.5 beats/min at 4 hours for 4 mg of xylazine/kg. The lowest mean ± SE respiratory rate for the medetomidine and xylazine treatments was 24.6 ± 1.5 breaths/min at 4 hours for 160 µg of medetomidine/kg and 28.4 ± 3.6 breaths/min at 4 hours for 4 mg of xylazine/kg. Respiratory arrest was not observed in any cats.

Diuretic effects—A diuretic effect was found for all doses of both medetomidine and xylazine, compared with results for the baseline (time 0) values **(Figure 1)**. For both the medetomidine and xylazine treatments, peak diuresis was 3 to 4 hours after injection. This diuretic effect persisted up to 5 hours after injection. Xylazine had a significant dose effect on the urine volume from 0.5 to 6 hours, but medetomidine did not, which indicated that xylazine, but not medetomidine, induced diuresis in a dose-dependent manner at the administered doses. Similar results were observed for total urine volume from 0.5 to 2, 0.5 to 3, 0.5 to 4, and 0.5 to 5 hours after injection for both drugs.

The urine specific gravity decreased significantly for both medetomidine and xylazine, compared with the baseline values, except when cats received 40 µg of medetomidine/kg and 0.5 mg of xylazine/kg **(Figure 2)**. The lowest urine specific gravity was detected 3 to 4 hours after injection of medetomidine and 2 to 4 hours after injection of xylazine. These decreases in urine specific gravity corresponded closely with the increase in urine volume for both medetomidine and xylazine. Urine pH did not change significantly for any of the treatments.

Urine osmolality decreased significantly after injection of both medetomidine and xylazine, compared with the baseline values (Figure 2). The lowest urine osmolality was detected 2 to 4 hours after injection of medetomidine and 3 to 4 hours after injection of xylazine. These decreases in urine osmolality corresponded

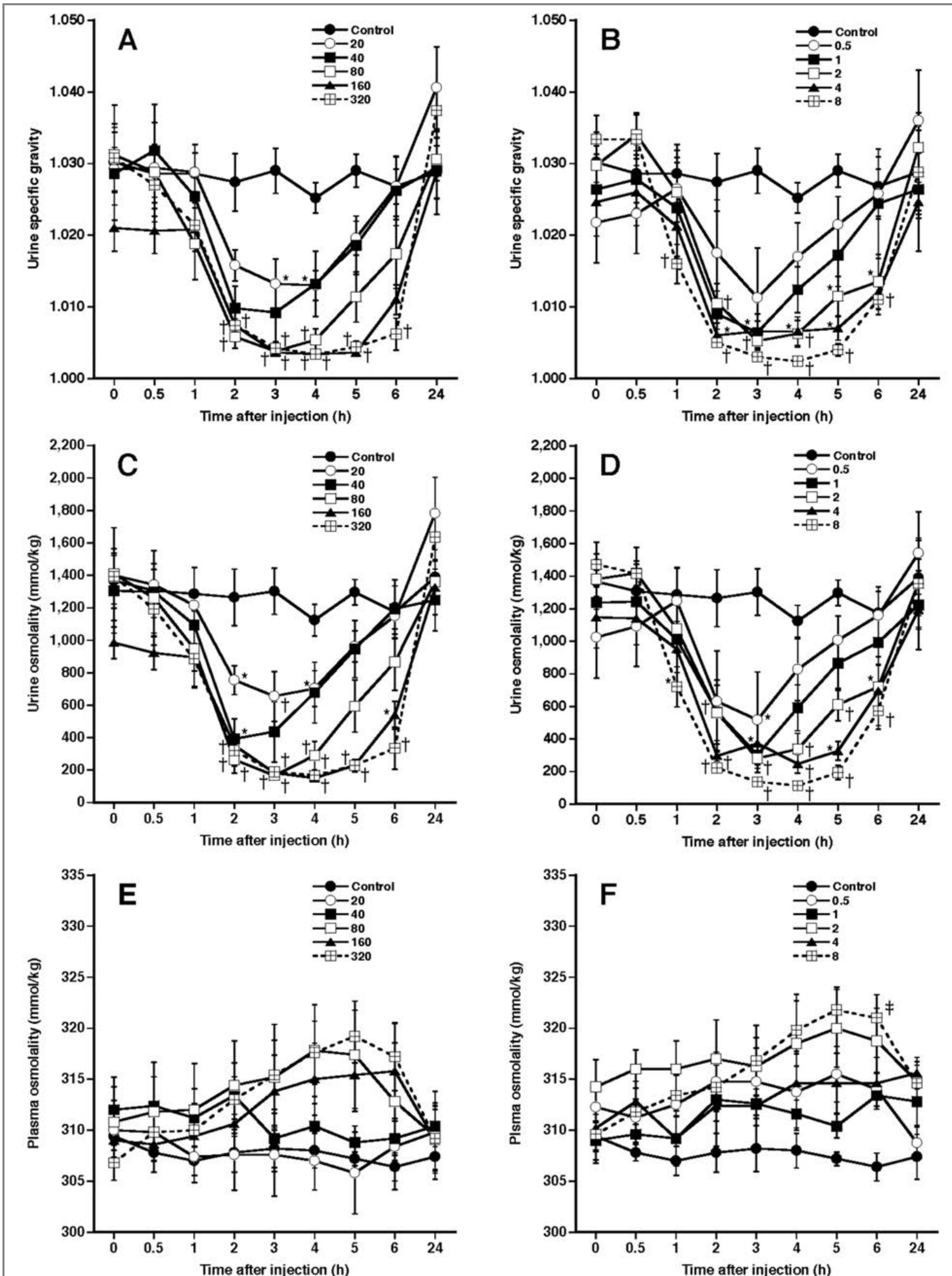

Figure 2—Mean ± SE urine specific gravity (A and B), urine osmolality (C and D), and plasma osmolality (E and F) for 5 cats after injection of saline solution (control treatment) or various doses of medetomidine (µg/kg; A, C, and E) or xylazine (mg/kg; B, D, and F). ‡Within a time point, values differs significantly ($P < 0.05$) from the value for the control treatment. *See* Figure 1 for remainder of key.

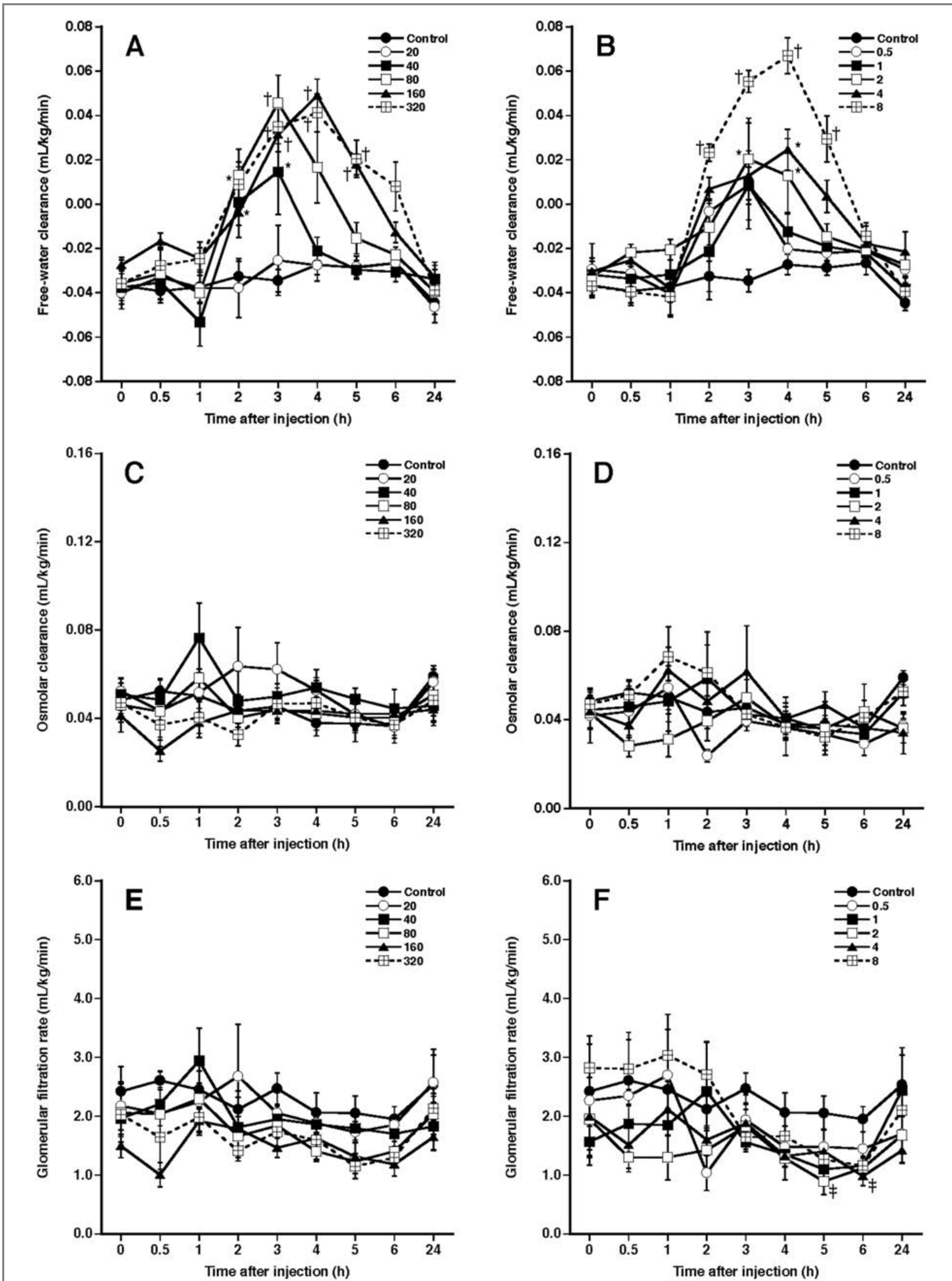

Figure 3—Mean ± SE free-water clearance (A and B), osmolar clearance (C and D), and GFR (E and F) for 5 cats after injection of saline solution (control treatment) or various doses of medetomidine (µg/kg; A, C, and E) or xylazine (mg/kg; B, D, and F). *See* Figures 1 and 2 for remainder of key.

closely with the increase in urine volume for both medetomidine and xylazine.

Plasma osmolality did not change significantly for any of the treatments, compared with the baseline values. However, the value at 6 hours after injection of 8 mg of xylazine/kg was significantly increased, compared with the value at 6 hours after injection of saline solution (control treatment; Figure 2). Free-water clearance increased significantly for both the medetomidine and xylazine treatments, compared with baseline values, except when cats received 20 µg of medetomidine/kg, 0.5 mg of xylazine/kg, and 1 mg of xylazine/kg (**Figure 3**). Peak free-water clearance was detected 3 to 4 hours after injection of both medetomidine and xylazine. Osmolar clearance did not change significantly for any of the treatments, compared with the baseline values or the values for the control treatment. Although the GFR did not change significantly for any of the treatments, compared with the baseline values, the values at 5 hours after injection of 2 mg of xylazine/kg and 6 hours after injection of 4 mg of xylazine/kg were significantly decreased, compared with the values for the control treatment at those time points. Both osmolar clearance and GFR did not have dose-dependent changes for the medetomidine and xylazine treatments.

Plasma AVP concentrations decreased (albeit not significantly) initially (0.5 to 4 hours) at the highest dose of medetomidine and increased thereafter (5 to 6 hours) for both the medetomidine and xylazine treatments, compared with the baseline values (**Figure 4**). A significant difference was detected 6 hours after injection only when cats received 160 µg of medetomidine/kg. Results of linear regression of the AUC data for plasma AVP concentrations from 0 to 3 hours were significant (*P* = 0.01) for the medetomidine treatments but not for the xylazine treatments. Similar results were obtained from the AUC data for plasma AVP concentration from 0 to 2, 0 to 4, 0 to 5, and 0 to 6 hours after injection for both drugs.

Although plasma sodium concentrations did not change significantly for any of the treatments, compared with the baseline values, the value at 6 hours after injection of 8 mg of xylazine/kg was significantly increased, compared with the value at 6 hours after injection of the control treatment (**Figure 5**). Plasma potassium and chloride concentrations did not change significantly for any of the medetomidine or xylazine treatments, compared with the baseline values or values for the control treatment. Fractional clearances of all electrolytes typically increased or increased significant-

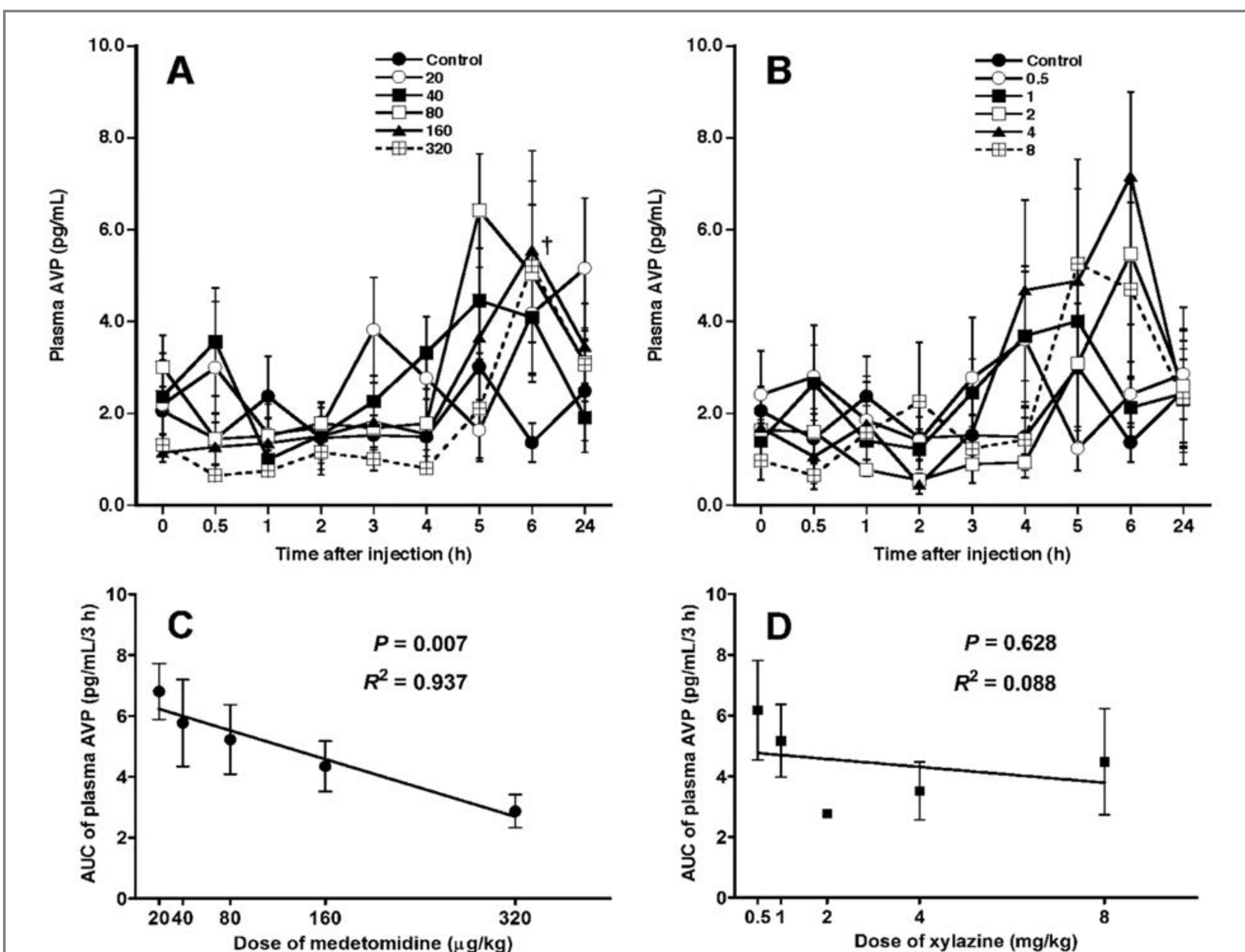

Figure 4—Mean ± SE plasma AVP concentration for 5 cats after injection of saline solution (control treatment) or various doses of medetomidine (µg/kg; A) or xylazine (mg/kg; B) and linear regression of the AUC data for plasma AVP concentration after injection of the various doses of medetomidine (C) or xylazine (D). *See* Figure 1 for remainder of key.

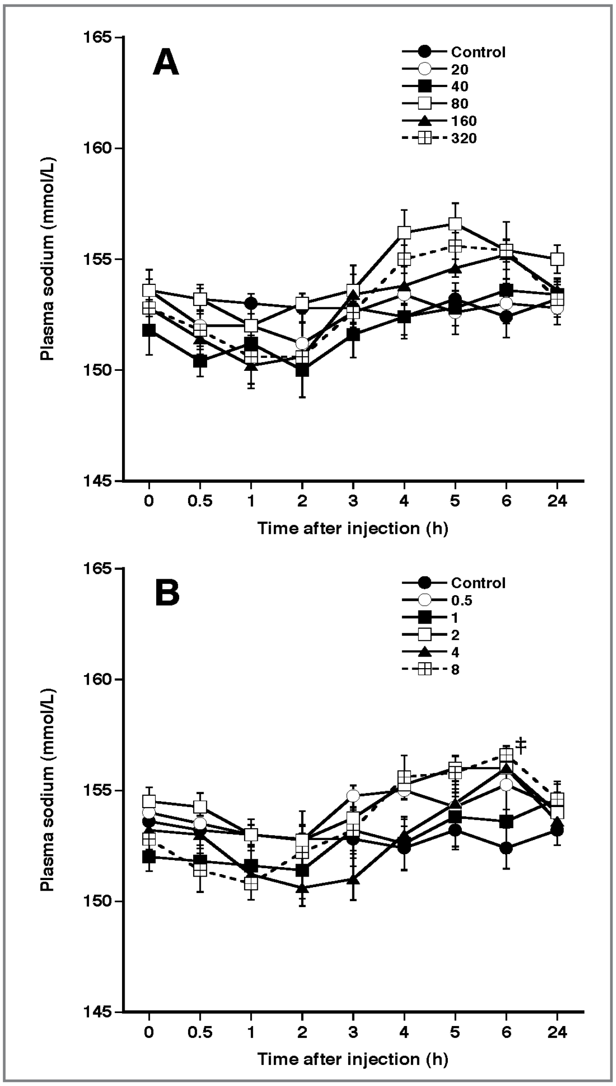

Figure 5—Mean ± SE plasma sodium concentration for 5 cats after administration of saline solution (control treatment) or various doses of medetomidine (µg/kg; A) or xylazine (mg/kg; B). *See* Figure 2 for remainder of key.

ly 5 to 6 hours after injection of higher doses of both medetomidine and xylazine (**Figure 6**). At 6 hours after injection, there was a significant increase in potassium concentration when cats received 4 mg of xylazine/kg and a significant increase in all electrolyte concentrations when cats received 8 mg of xylazine/kg.

Discussion

Analysis of results for the study reported here revealed that IM administration of both medetomidine and xylazine significantly increased urine volume in healthy cats. To our knowledge, this is the first study in which a diuretic effect of both medetomidine and xylazine in cats has been reported. These effects are consistent with results of studies on medetomidine-induced diuresis in dogs[13,14,16,20] and rats[9] and xylazine-induced diuresis in dogs,[13,15] cattle,[11] horses,[17,21–23] and rats.[24–27] The present study also found that the diuretic effects of medetomidine were not a dose-dependent phenomenon at the evaluated doses; however, xylazine induced dose-dependent diuresis in cats. The differences in the dose-dependent effects between medetomidine and xylazine were similar to the findings of another study[13] in dogs conducted by our laboratory group. Because medetomidine is a more selective and specific α_2-adrenoceptor agonist than is xylazine, the different diuretic responses to both drugs could not be explained by the difference in the affinity of α_2-adrenoceptors. Therefore, this difference may have been attributable to the distinct α_2-adrenoceptor and α_1-adrenoceptor selectivity or the imidazoline-receptor selectivity for the 2 drugs, as has been suggested in dogs.[13]

In the present study, urine specific gravity and urine osmolarity decreased in proportion with the increase in free-water clearance after medetomidine and xylazine administration. These changes were detected at the same time as the increase in urine volume induced by both drugs. In addition, the present study revealed that the osmolar clearance did not change significantly for both drugs. In rats, osmolar clearance increases after administrations of clonidine[7] and xylazine.[27] Furthermore, it has been suggested that the osmotic diuresis caused by hyperglycemia and glucosuria attributable to xylazine-induced inhibition of insulin release are involved in the diuretic action of xylazine in cattle and ponies.[11,22] However, our results in cats indicated that the diuretic effects of medetomidine and xylazine can largely be explained by a decrease in the absorption of water in the renal tubules of the kidneys.

A significant decrease in GFR, compared with the value for the control treatment, was detected 5 hours after injection of 2 mg of xylazine/kg and 6 hours after injection of 4 mg of xylazine/kg. However, there were no significant differences, compared with the baseline values, for any of the treatments. In dogs, GFR decreases after IM administration of medetomidine, and it has been suggested that this effect may be the result of a decrease in renal blood flow.[20] Results of the present study indicated that there was a significant decrease in GFR after the peak diuretic effect. Therefore, this effect may have been attributable to a secondary change resulting from dehydration by diuresis.

In contrast, urine pH did not change significantly for any of the treatments in the present study. Studies on cattle[11] and dogs[13,16] have found that urine pH decreased after medetomidine or xylazine administration, which may have been attributable to arterial hypercapnia.

An increase in plasma osmolarity, compared with the control value, was detected 6 hours after injection of the highest dose of xylazine, but the increase was not significant for any of the treatments. Serum or plasma osmolarity increases after medetomidine or xylazine administration, probably as a result of renal loss of water in dogs,[13,16] but there is no change in osmolarity after xylazine injection in horses.[21,22] Differences between animal species may be responsible for differences in renal function. In addition, cats in the present study received an infusion of lactated Ringer's solution the night preceding treatment. This infusion may have influenced the changes in urine pH and plasma osmolality in the present study. The precise reasons for the differences among the animal species for the variables are unknown.

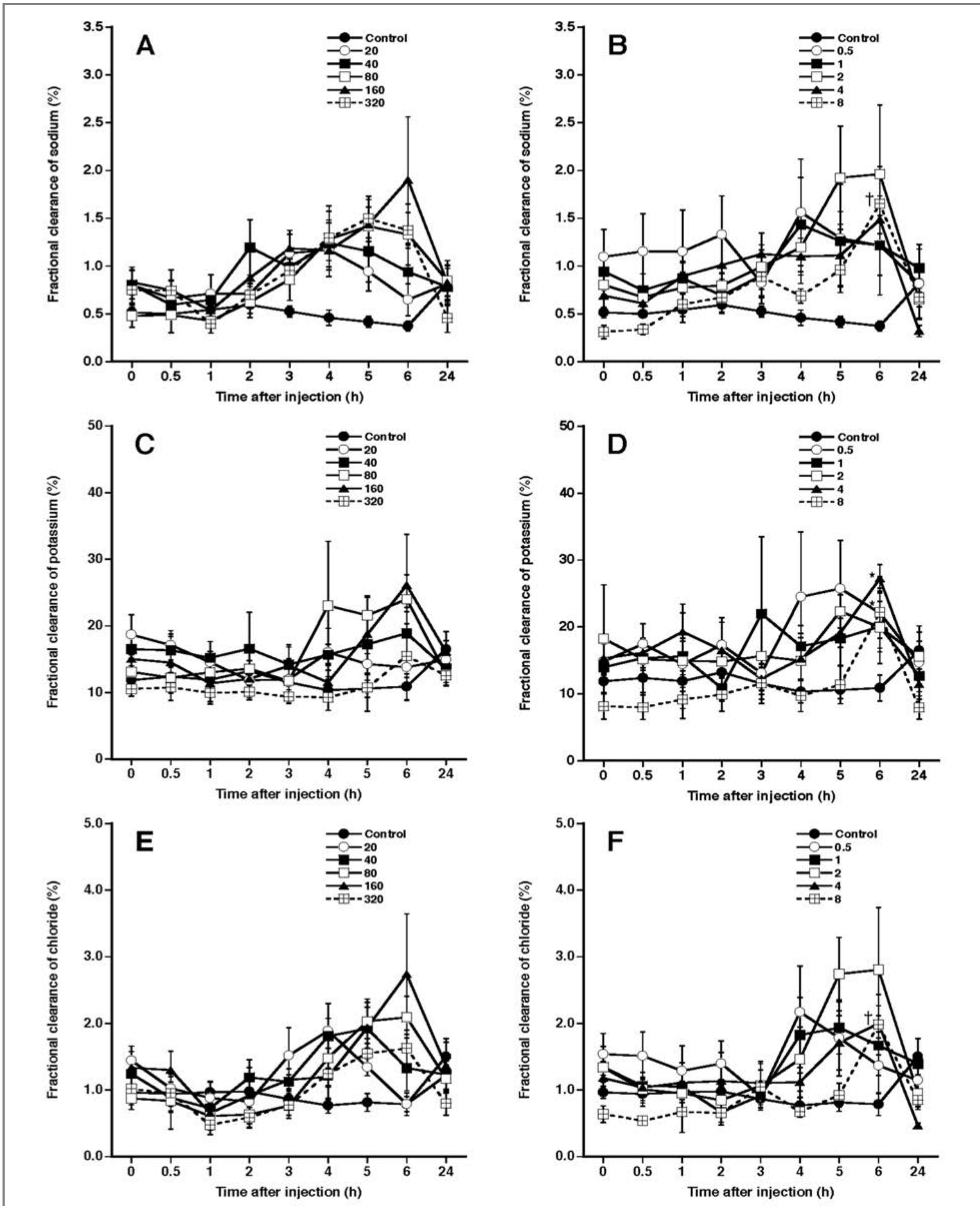

Figure 6—Mean ± SE fractional clearance of sodium (A and B), potassium (C and D), and chloride (E and F) for 5 cats after administration of saline solution (control treatment) or various doses of medetomidine (µg/kg; A, C, and E) and xylazine (mg/kg; B, D, and F). *See* Figure 1 for remainder of key.

In another study[13] conducted by our laboratory group on dogs, we found that medetomidine significantly decreased plasma AVP concentrations, whereas xylazine did not significantly alter the AVP concentrations. The present study revealed that plasma AVP concentrations did not change significantly during the diuretic period after administration of medetomidine and xylazine in cats, although it typically decreased initially after injection of the highest dose of medetomidine. Investigators in 1 study[28] found that cats have a higher osmotic threshold than do other animals. In the present study, the cats received Ringer's solution to maintain urine volume during sample collection by increasing extracellular fluid compartments; therefore, this infusion may have influenced changes in plasma AVP concentrations because the cats received a high sodium load. It has also been reported that α_2-adrenoceptor agonists (eg, clonidine, medetomidine, and dexmedetomidine) inhibit the secretion of AVP from the pituitary gland and thereby decrease plasma AVP concentrations in dogs.[4,5,20,29,30] One in vitro study[6] revealed that α_2-adrenoceptor agonists (eg, epinephrine, clonidine, guanabenz, and oxymetazoline) inhibit AVP-stimulated accumulation of cAMP in the collecting tubes of rats but not of dogs, rabbits, or pigs. Furthermore, the increase in free-water clearance after clonidine administration is associated with a reduction in whole kidney aquaporin-2 mRNA and independent of the changes in vasopressin activity in rats.[7] Therefore, the increase in urine volume detected in the study reported here may have been independent of the changes in plasma AVP concentrations in cats.

In the present study, linear regression analysis of the AUC data revealed that medetomidine decreased plasma AVP concentrations in a dose-dependent manner, whereas xylazine did not. These results were consistent with those of a study[13] in dogs. These findings indicated that medetomidine, in contrast to xylazine, more clearly inhibited AVP release. Although the precise mechanism for the difference between medetomidine and xylazine is unknown, it may be partly attributable to differences in receptor selectivities in that medetomidine has affinity for the imidazoline receptor[3] and also has α_2-adrenoceptor selectivity that is approximately 10-fold as high as that of xylazine.[2] Investigators in 1 study[31] reported that imidazoline α_2-adrenoceptor agonists (eg, clonidine, moxonidine, and dexmedetomidine) mediate their actions via both α_2-adrenoceptors and imidazoline receptors.

An increase in plasma sodium concentrations, compared with the value for the control treatment, was detected 6 hours after injection of the highest dose of xylazine; however, there were no significant increases, compared with the baseline values, for any of the treatments. This change is associated with the increase in plasma osmolality. In contrast, plasma potassium and chloride concentrations did not change significantly after medetomidine and xylazine injections in the present study. These effects differ from the results of a study[13] on dogs. In the present study, the fractional clearances of sodium, potassium, and chloride typically increased or increased significantly 4 to 6 hours after medetomidine and xylazine injections in cats. The increase in fractional clearance or excretion of electrolytes in cats is consistent with results of studies on dogs,[16] horses,[21,22] and rats.[9,25–27] Although there is a simultaneous increase in the excretion of sodium and potassium with the increase in urine volume in rats,[9,25–27] results of the present study indicated that there was a significant increase in plasma sodium concentrations and fractional clearance of electrolytes after the peak diuretic effect for high doses of xylazine. This effect may have been attributable to a compensatory response to the increase in the plasma electrolyte concentrations in cats.

In the present study, diuretic effects for a wide range of doses of medetomidine and xylazine were evaluated for the purpose of determining a dose-related effect in clinically normal cats. The lower doses of medetomidine (20 to 40 µg/kg) and xylazine (0.5 to 1 mg/kg), which would be recommended clinically, had mild and similar diuretic effects in this study. It appeared that the diuretic effects induced by both drugs at the lower doses would not pose problems in healthy cats. Given that both drugs cause diuresis, even when the drugs are administered at lower doses, careful consideration is needed for the use of either drug in cats with urinary tract obstruction, hypovolemia, or dehydration. In contrast, this study revealed that administration of both medetomidine and xylazine at higher doses induced profound and prolonged diuresis and that the diuretic effect of medetomidine was also accompanied with a change in AVP concentrations. Therefore, the use of higher doses of both drugs is not recommended for clinical practice and requires concurrent administration of fluids.

In the present study, both medetomidine and xylazine induced profound diuretic effects in healthy cats. At the evaluated doses, xylazine induced a dose-dependent diuretic response, whereas medetomidine induced a diuretic response that was not dose dependent. The AUC of plasma AVP concentrations after administration of medetomidine, in contrast to that after administration of xylazine, decreased in a dose-dependent manner, but this was not related to diuresis. The present study further revealed that changes in plasma AVP concentrations, GFR, and osmolar clearance are not part of the diuretic effects of either drug in cats. Other factors, such as the difference in α_2- and α_1-adrenoceptor selectivity or imidazoline receptor selectivity on the renal system, may be involved in the diuretic mechanism.

a. StatMate3, ATMS, Tokyo, Japan.
b. GraphPad Prism software, GraphPad Software Inc, La Jolla, Calif.

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