EFFECT OF METHOXYFLURANE ANESTHESIA ON RENAL CONCENTRATING ABILITY OF DOGS

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PREFACE

This study characterizes the effects of methoxyflurane anesthesia on renal concentrating ability and response to antidiuretic hormone (ADH) challenge in dogs under conditions of dehydration and overhydration. The information gained is useful in evaluating the renal functional status of research animals or clinical patients exposed to methoxyflurane anesthesia.

I wish to express my sincere gratitude to all the people who have assisted me in this project. In particular, I am indebted to Dr. Ron Tyler, my thesis adviser and the inspiration for this project, not only for his guidance, much needed encouragement, and assistance on this project, but also for going out of his way to get me started in clinical pathology. I'm not sure what I did to deserve the truly enviable position that I have found myself in for the past year (probably nothing), but it has been tremendous!

I'd also like to thank Dr. Rick Cowell for his ideas and assistance in this project as well as others during the past 12 months.

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INTRODUCTION

The ability of the kidneys to resorb free water during periods of dehydration is important in their function of maintaining body water homeostasis. Hypotension and/or an increase in plasma osmolality results in increased release of antidiuretic hormone (ADH). Antidiuretic hormone binds to receptors in the collecting ducts and results in resorption of free water from the tubular lumen. This returns free water to the plasma and concentrates the urine.

In 1979, Hardy and Osborne reported the mean maximal urine specific gravity (USG) of 20 dogs following water deprivation to be 1.062 $\pm$ 0.007 and suggested that the production of urine with a specific gravity of less than 1.048 when slight dehydration is detectable indicates nephron dysfunction.[3] In subsequent reports, Osborne and Polzin have suggested the more conservative limit of 1.030 as the minimum USG indicating adequate renal function in the dog.[1,2] This level has become widely accepted.[4-9] Therefore, dogs with normal renal concentrating ability are expected to excrete urine with a specific gravity of greater than or equal to 1.030 when mildly dehydrated. Dogs that excrete urine with an inappropriately low urine specific gravity (less than 1.030) while dehydrated are considered to have decreased renal concentrating ability.[2,5]

The most common cause of decreased renal concentrating ability is primary renal failure, however, there are other causes. Diabetes insipidus, Addison's disease, Cushing's disease, severe hyponatremia,

pyometra, hepatic failure, postobstructive diuresis, potassium deficiency, diuretics, alcohol and corticosteroids[5,9] all can interfere with concentrating ability, even with normally functioning kidneys. It is important to recognize these exceptions since they do not involve renal pathology and, therefore, warrant a different treatment and prognosis.

Methoxyflurane, halothane, and methohexital have been reported to inhibit ADH stimulated free water transport in vitro.[10,25] These reports are based on studies using the toad urinary bladder as a model for the mammalian kidney collecting duct epithelium. Extrapolation of the results of these studies to in vivo clinical situations suggests another condition, anesthesia, which might cause decreased renal concentrating ability without renal failure and, therefore, lead to misdiagnosis if its effect is not considered. Supporting this are the results of studies which have shown transient polyuria in dogs following methoxyflurane anesthesia.[17-20]

However, reports of human clinical studies appear to contradict this premise. Studies of water loaded human volunteers demonstrated a marked antidiuresis, characterized by change from positive to negative free water clearance, a marked reduction in urine volume and an increase in urine osmolality (U_{osm}), following induction of anesthesia.[11-13]

The purpose of this study was to examine and characterize the effect of methoxyflurane anesthesia on the renal concentrating ability of the dog; specifically, to determine if methoxyflurane anesthesia causes decreased renal concentrating ability and, if it does, to

determine the magnitude and duration of this decrease, and its responsiveness to ADH administration.

MATERIALS AND METHODS

Five clinically normal adult intact male mongrel dogs weighing 15 to 20 kg were obtained through the laboratory animal resources unit. The animals were determined to be healthy on the basis of physical examination, complete blood count (CBC), serum chemistry profile, urinalysis and demonstration of the ability to concentrate urine to a specific gravity of greater than 1.047 when water was withheld. They were housed in individual indoor runs and fed a commercial dry dog food. The study consisted of three phases. Animals were given a minimum of two weeks recovery between each phase of the experiment. A urinalysis was performed during the recovery period after phase 1 and phase 2 to monitor for signs of cystitis and/or pyelonephritis which might result from catheterization and to ensure continued ability to adequately concentrate urine.

Phase 1: Urine concentrating ability of dehydrated animals during and following methoxyflurane anesthesia

Water was withheld for 24 to 36 hours, as necessary, to result in the production of concentrated urine, and food was withheld the day of the procedure. A surgical plane of methoxyflurane anesthesia was induced by mask followed by tracheal intubation; the animals were placed in lateral recumbency on heating pads and covered to help maintain body temperature. Depth of anesthesia was assessed by corneal reflex, jaw tone and response to toe pinch. Body temperature

was monitored every hour. No fluids were administered. An 8- to 10-french, rubber, urinary catheter was placed for the collection of urine samples; serum samples were obtained by jugular venipuncture. Serum and urine samples were collected prior to anesthesia (0 time) and after 1, 2, 3, and 4 hrs of anesthesia. Following 4 hrs of anesthesia at a surgical plane, the dogs were allowed to recover from anesthesia. Serum and urine samples were obtained at 1, 8, and 24 hrs after cessation of anesthesia.

Specific gravity, osmolality, creatinine (cr), sodium (Na^+) and potassium (K^+) were measured for each urine sample and Na^+, K^+, cr and osmolality were determined for each serum sample. Fractional excretion (Fe) of Na^+ and K^+ were calculated for each sample using the formula

$$\text{Frac. excretion}(x)=[x]_{urine}/[x]_{serum} \times [cr]_{serum}/[cr]_{urine} \times 100.$$

Whole blood (3 mls) was collected in EDTA tubes for CBCs at 0 time and at the end of the anesthetic period. In addition to the above tests, chemistry profiles were run on each dog at 0 time and at the end of 4 hrs of anesthesia.

Specific gravity was determined by refractometry. Osmolality was determined using a Wescor D100b vapor pressure osmometer. Serum chemistry values were determined on a DuPont ACA2 automated clinical analyzer and CBCs were performed on a Coulter counter model S.

Phase 2: ADH response test

Animals were handled similarly to phase 1, but the duration of anesthesia was extended and at the beginning of the fifth hour of anesthesia, an ADH response test was performed. The animal received

2.2 ml/kg (1 ml/lb) of a solution containing 5 units of ADH in one liter of 5% Dextrose for a total dose of 11 microunits/kg (5 microunits/lb) as suggested by Hardy[3]. This 5% dextrose/ADH solution was given as a constant drip over 60 minutes. Additional serum and urine samples were collected 30, 60, and 90 minutes after induction of the ADH drip and assayed for osmolality, Na^+, K^+, Cr and specific gravity.

Phase 3: FREE WATER CLEARANCE AND ADH RESPONSIVENESS BEFORE AND AFTER ANESTHESIA IN WATER LOADED DOGS

Animals were given a rapid IV drip of 5% Dextrose until the urine specific gravity was 1.005 or less. At this time, the drip rate was slowed to and maintained at 2.2 ml/kg/hr (1 ml/lb/hr) for a period of 60 minutes to ensure that USG remained less than 1.005. A presample was obtained by collecting all urine produced over a 15 minute period; a matching serum sample was taken in the middle of this period. A preanesthetic ADH response test was then begun. The rate of fluid administration remained 2.2 ml/kg/hr using the 5% dextrose/ADH solution. The 5% dextrose/ADH drip was maintained for 1 hour delivering a dose of 11 microunits of ADH/kg (5 microunits/lb) similar to phase 2. Two 30 minute urine samples were collected during the 5% dextrose/ADH infusion; serum samples were collected with each of the urine samples. At the end of one hour of 5% dextrose/ADH infusion, the infusion of 5% dextrose alone was resumed and continued until USG returned to 1.005 or less.

The animal was then anesthetized with methoxyflurane by mask, intubated, placed on a heating pad and covered. The urine, along with

a matched serum sample, was collected every thirty minutes for two hours. At the beginning of the third hour of anesthesia, the ADH challenge was repeated. Urine volume, specific gravity, osmolality, and serum osmolality were measured and free water clearance was calculated for each sample. Following phase three, the dogs were euthanatized and post-mortem examination including renal histopathology was performed.

Mean USG, U_{osm},and FeNa+ were compared for all time periods against the presample (Phase 1 and 2) or against the maximal preanesthetic ADH challenge value (Phase 3) using a paired t-test[29].

RESULTS

PHASE 1:

Urine specific gravity (USG) and urine osmolality (U_{osm}) decreased rapidly after induction of anesthesia. The decrease was statistically significant for both parameters after the first hr and continued to decrease during the 4 hr anesthetic period (figure 1). The mean USG and U_{osm} for the various time periods are given in Table I. The average USG at 4 hrs of anesthesia and at the 1 hr post anesthetic period were both below 1.030 ($x=1.028 \pm 0.003$; range=1.020-1.035 and $x=1.026 \pm 0.003$; range=1.016-1.032, respectively). The USG of the 8 hr post anesthetic period samples ($x=1.030 \pm 0.002$; range=1.025-1.034) remained significantly lower than the preanesthesia samples ($x=1.050 \pm 0.002$; range=1.045-1.055), but by 24 hrs post anesthesia, the difference was no longer statistically significant. The lowest urine specific gravity obtained was 1.016 in the 1 hr post anesthetic period sample. Presample urine osmolalities

Phase 1 Changes in urine specific gravity of dehydrated dogs during and following methoxyflurane anesthesia

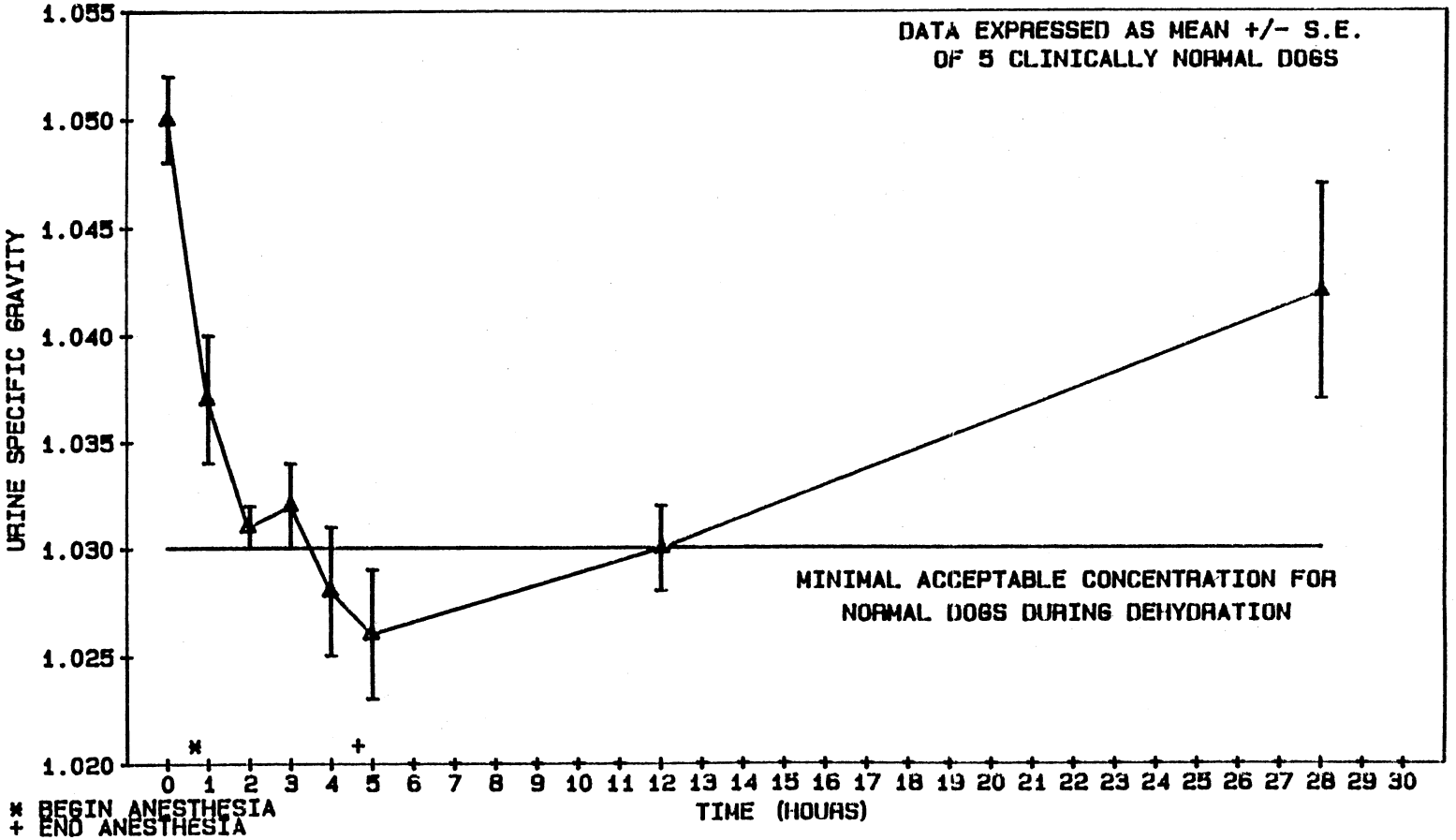


TABLE I

CHANGES IN URINE CONCENTRATIONS IN DEHYDRATED DOGS DURING METHOXYFLURANE ANESTHESIA

Phase One

Variable		Time (hr) 0	1	2	3	4[a]	5	12	28
USG	MEAN	1.050	1.037*	1.031*	1.032*	1.028*	1.026*	1.030*	1.042
	S.E.	0.002	0.003	0.001	0.002	0.003	0.003	0.002	0.005
Uosm	MEAN	1908	1297*	1091*	1082*	816*	915*	1102*	1577
	S.E.	110	87	53	132	146	119	94	164

Phase Two

Variable		Time (hr) 0	1	2	3	4[b]	5	12	28
USG	MEAN	1.058	1.043*	1.039*	1.033*	1.036*	1.036*	1.035*	1.034*
	S.E.	0.003	0.001	0.002	0.001	0.002	0.003	0.003	0.002
Uosm	MEAN	2094	1433*	1275*	1165*	1245*	1291*	1237*	1156*
	S.E.	120	88	64	84	124	117	109	91

[a]=anesthesia ended after obtaining this sample.
[b]=ADH challenge started after obtaining this sample.
*=significantly lower than 0 time ($p < .05$)

were all greater than 1700 (x=1908 ± 110; range=1726-2326). They dropped rapidly following anesthesia; the nadir (x=816 ± 146) being at the fourth hour of anesthesia. At this time, osmolality ranged from 413 to 1153 mosm/liter. Following recovery from anesthesia, urine osmolality increased such that, by 24 hrs following anesthesia it was no longer statistically different than preanesthesia sample values.

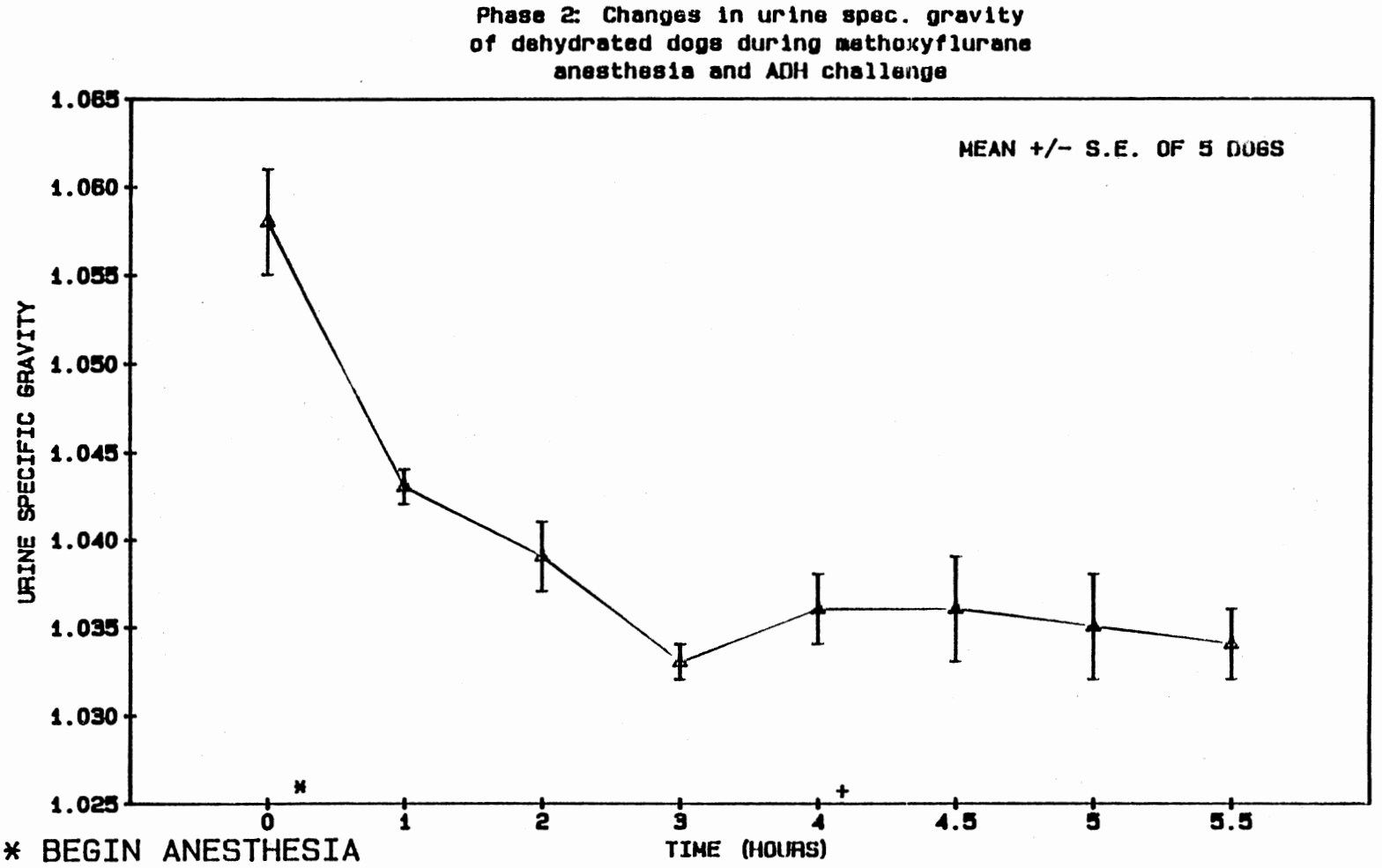
Dog #1291 became markedly hyperkalemic (serum potassium concentration of 8.5 mEq/l) after 4 hrs of anesthesia. This was associated with a severe respiratory acidosis (venous pH= 6.94, P_{co_2}=122.8, P_{o_2}=357, HCO_3=26.6 mEq/l). The serum K+ values of the other dogs remained within the normal range.

Three of the five dogs became hypothermic (body temp. less than 99°F). The other dogs maintained normal body temperature (100-103°F).

PHASE 2:

A significant drop in USG and U_{osm} was again seen following induction of anesthesia (Table I). Mean USG was reduced from 1.058 ± 0.003 (range=1.053-1.068) prior to anesthesia to a nadir of 1.033 ± 0.001 (range=1.027-1.035) after three hrs of anesthesia. The mean osmolality dropped from 2094 ± 120; (range=1778-2560) to 1165 ± 84; (range=920-1427) at three hrs of anesthesia. There was no significant increase in USG or U_{osm} following administration of an ADH drip (Table I, Fig. 2).

Dog #1291 became moderately hyperkalemic, again, with a serum K+ level of 7.88 mEq/L after three hours of anesthesia. Venous pH at this time was 7.08 with a PCO_2 of 84 and a bicarbonate of 25.3 mEq/l. The serum K+ levels were within the normal range in the other



* BEGIN ANESTHESIA

+ END ANESTHESIA

dogs, although most of the other dogs were mildly to moderately acidemic (venous pH range 7.18-7.4).

Two of the five dogs became hypothermic.

PHASE 3:

Results of phase 3 are given in Table II and Fig. 3. During the initial water load, the mean USG was 1.002 ± 0.0005 (range=1.001 to 1.004) and the mean free water clearance was 3.4 ± 0.9 ml/min (range=1.28-6.89) As expected, the ADH challenge resulted in a marked increase in USG, drop in urine volume and conversion to negative free water clearance. During the second thirty minute collection period after the start of the ADH challenge, mean USG was 1.036 ± 0.002 (range=1.030-1.043) and the free water clearance was -0.71 ± 0.35 ml/min (range= -0.07to -2.12). Urine specific gravity decreased to 1.001 ± 0 and free water clearance increased to 2.99 ± 0.42 ml/min (range=2.08 to 4.76) within 1 to 2 hrs after cessation of the ADH drip.

Anesthesia resulted in changes similar to those seen during ADH challenge. One hour after induction of anesthesia, mean USG was 1.026 ± 0.002 (range=1.020 to 1.030) and free water clearance was -0.52 ± 0.16 ml/min. (range=0.01 to -1.04). The 90 and 120 minute values were not statistically different from those at one hour.

The ADH challenge performed at the beginning of the third hour of anesthesia did not result in any statistically significant changes in USG, U_{osm} or free water clearance.

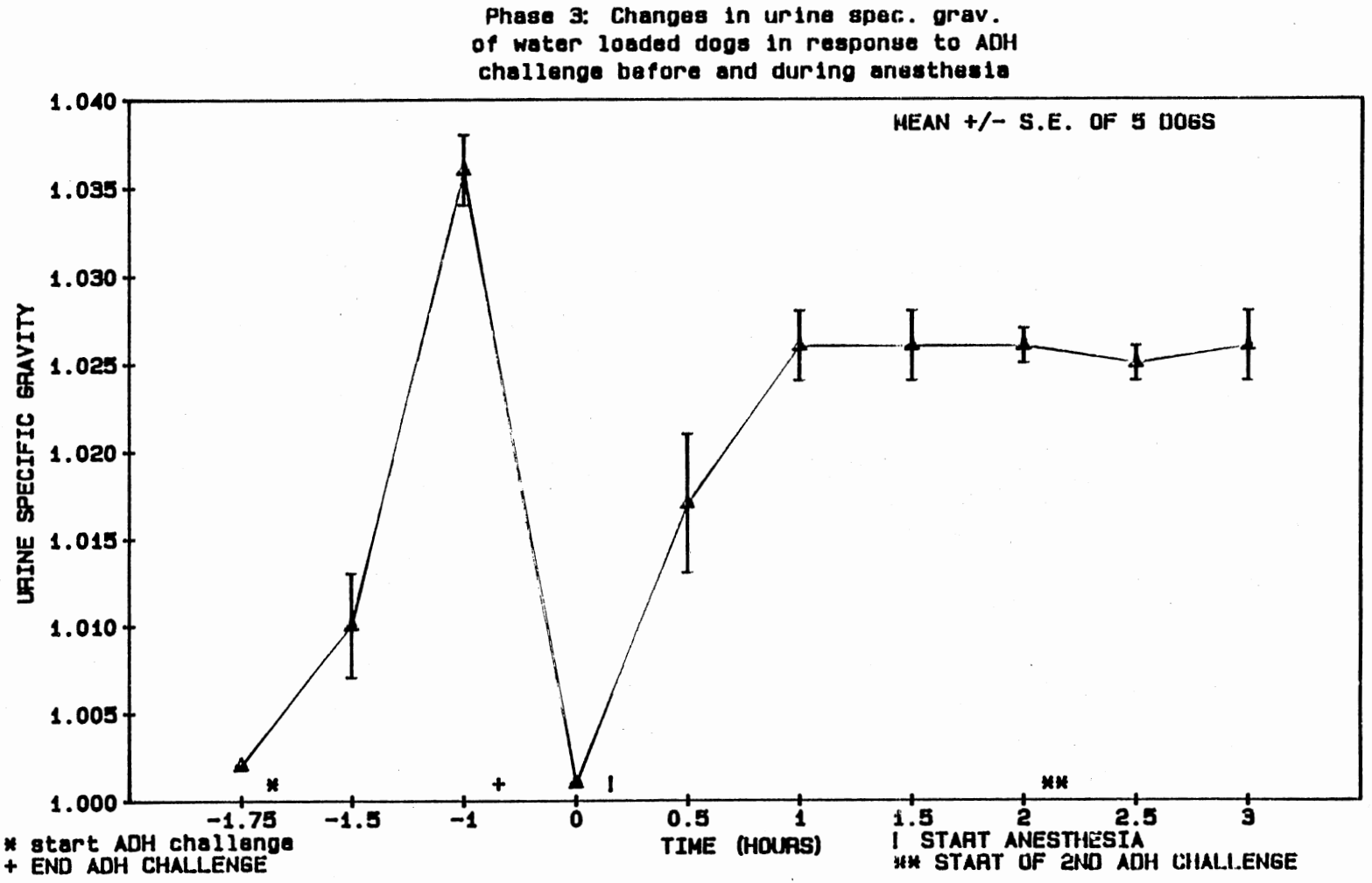
The USG and U_{osm} from the ADH challenge performed during anesthesia were generally lower than the ADH challenge on unanesthetized dogs. Only one of the 5 dogs was able to attain USG

TABLE II

RESPONSE OF WATER LOADED DOGS TO ADH CHALLENGE
BEFORE AND DURING ANESTHESIA

	PHASE 3									
	Time (hr)									
Variable	-1.75[a]	-1.5	-1[b]	0[c]	0.5	1	1.5	2[d]	2.5	3
USG MEAN	1.002	1.010	1.036	1.001	1.017*	1.026*	1.026*	1.026*	1.025*	1.026*
S.E.	0.000	0.003	0.002	0.000	0.004	0.002	0.002	0.001	0.001	0.002
Osmo MEAN	72	293	1329	74	505*	823	872*	900	918*	974*
S.E.	19	117	89	10	178	161	92	92	75	113

a=ADH challenge started following this sample.
b=ADH challenge ended following this sample.
c=Anesthesia started following this sample.
d=Second ADH challenge started following this sample.
*=Significantly lower than time -1 hr. ($p < .05$)


Phase 3: Changes in urine spec. grav.
of water loaded dogs in response to ADH
challenge before and during anesthesia
MEAN +/- S.E. OF 5 DOGS
URINE SPECIFIC GRAVITY
1.040
1.035
1.030
1.025
1.020
1.015
1.010
1.005
1.000
-1.75
-1.5
-1
0
0.5
1
1.5
2
2.5
3
TIME (HOURS)
* start ADH challenge
+ END ADH CHALLENGE
I START ANESTHESIA
** START OF 2ND ADH CHALLENGE

and U_{osm} levels during the ADH challenge while anesthetized that were equal to preanesthetic ADH challenge values. The urinalyses performed following phase 1 and phase 2 did not reveal evidence of urinary tract infection. All dogs were able to concentrate to a specific gravity of greater than 1.047 between phases.

Serum chemistry profiles run prior to and at 4 hours of anesthesia during phase 1 and phase 2 were within normal limits other than the serum K+ values previously mentioned.

Results of the fractional excretions of Na+ and K+ measured during phase 1 are given in Table III. There was no statistically significant increases in either parameter during the four hours of anesthesia and the values were consistent with those previously reported for normal dogs.[25]

DISCUSSION

Induction and maintenance of anesthesia with methoxyflurane in dogs during water deprivation was associated with a rapid drop in USG and U_{osm}. This drop was statistically significant in the first group of samples examined (after 1 hr of anesthesia) and remained so through the four hrs of anesthesia and for 8 hrs post anesthesia. At times during anesthesia, some dogs produced urine with a specific gravity below 1.030. Values as low as this could result in an erroneous evaluation of the patient's renal function.[2,5,9] The response was variable between dogs with one dog dropping to as low as 1.016, but all dogs showing a significant drop.

Similarly, urine osmolalities were in the range that could lead to misinterpretation. The urine osmolality from all dogs decreased to

TABLE III

FRACTIONAL ECRETIONS*

Variable		Time (hr) 0	1	2	3	4
Fe Na+	MEAN	0.38	0.29	0.42	0.26	0.18
	S.E.	0.08	0.07	0.12	0.09	0.03
Fe K+	MEAN	9	10.2	15.9	20.8	23
	S.E.	2.4	2.1	3.5	2.0	3.4

*Fractional excretions measured during Phase 1

below 1500 mosm/L by the second hour of anesthesia; one dog's U_{osm} decreased to 413 mosm/L. Hardy and Osborne have suggested that levels below 1700 mosm/l, when the animal is mildly dehydrated, may indicate nephron dysfunction.[3] Subjectively, the magnitude of decrease in USG and U_{osm} seemed to be positively correlated with the depth of anesthesia, however, neither blood nor end expiratory methoxyflurane concentrations were measured to confirm this impression.

The decrease in renal concentrating ability was further supported by the response of water loaded dogs to ADH challenge during anesthesia. The mean USG produced by anesthetized dogs in response to an ADH challenge was lower than the mean USG produced by the same dogs in response to an ADH challenge while unanesthetized.

In phase 2 of the study, the lowered USG was not responsive to administration of exogenous ADH indicating that the decreased renal concentrating ability was not caused by lowered plasma ADH concentrations. Failure of ADH challenge to increase USG and U_{osm} during Phase 3 of the experiment supports this tenant.

Failure of exogenous ADH to increase urine concentration and the anesthesia induced antidiuresis seen in water loaded dogs during phase three suggest that ADH release is maximally stimulated during methoxyflurane anesthesia. This conclusion is consistent with previous studies.[11-13] Studies by Deutsch, demonstrated a marked antidiuresis and rise in urine osmolality in humans following anesthesia with halothane and cyclopropane.[11-13] These effects were partially reversible upon administration of ethanol suggesting that they were mediated, at least in part, by ADH.[11,12] Increased blood

levels of ADH have been demonstrated during methoxyflurane anesthesia.[13]

Submaximal urine concentration during maximal ADH secretion and/or administration suggests the possibility of either decreased binding of ADH to its renal receptors, decreased tubular response to ADH binding, or decreased renal medullary tonicity.

Evidence of renal pathology was not found in any of the dogs in this study. Renal concentrating ability returned rapidly after each anesthetic period and histopathologic lesions were not found in the kidney. Fractional excretion of Na+ and K+ were measured during the four hrs of anesthesia of phase 1. Fractional excretion of Na+ is a measure of tubular handling of sodium which is commonly used in human medicine to monitor for acute tubular necrosis.[14,15] Although normal ranges are not well established for the dog, the mean values obtained in this study were comparable to reported normal values [25] and no statistically significant increases occurred during the anesthetic period.

These findings suggest that methoxyflurane anesthesia results in a consistent, temporary decrease in renal concentrating ability without evidence of renal pathology. The magnitude of the concentrating defect is sufficient to cause the misdiagnosis of renal disease and may possibly be correlated to depth of anesthesia, but this latter association was not evaluated. The decreased renal concentrating ability is not responsive to exogenous ADH administration. In fact, endogenous ADH appears to be maximally stimulated during methoxyflurane anesthesia impairing the animal's ability to clear free water. Recovery from anesthesia leads to a rapid reversal of impaired

renal concentrating ability with USG and U_{osm} values no longer significantly lower than presample values by 24 hrs after cessation of anesthesia. The opposing effects of impaired renal concentrating ability and stimulation of ADH release probably account for the apparently conflicting reports of renal response to methoxyflurane anesthesia.

No attempt was made to determine the mechanism of the renal concentrating defect, nor to determine whether the defect was unique to methoxyflurane or a result of physiologic changes associated with general anesthesia. Most dogs in the study became acidotic and some became hypothermic despite attempts to maintain normal body temperature. Neither of these conditions is likely to be the sole cause of the concentrating defect observed. Rose et al., in 1984, demonstrated that conscious dogs with hypercapnic acidosis (P_{co_2}= 53; pH=7.19) had no change in U_{osm} and the free water clearance became more negative.[16] "Cold diuresis" has been reported in humans and various animals.[26,27] In rats, exposure to cold ambient temperature results in increased urine volume and decreased urine osmolality.[26] It was suggested that this diuresis was the result of lowered endogenous ADH release secondary to systemic hemodynamic responses.[26] One study in dogs demonstrated a decreased ability to resorb free water during cold exposure; plasma ADH values in these animals were found to be increased.[27] Urine osmolalities were not reported. In the present study, all dogs had decreased renal concentrating ability during anesthesia, but not all of them became hypothermic. Also, the urine specific gravity and osmolality were still decreased at 8 hours post anesthesia and, although not measured

post anesthesia, it would be expected that body temperature would have returned to normal by this time.

In humans, it has been well documented that prolonged exposure to methoxyflurane anesthesia is associated with a nephrotoxicosis characterized by polyuria and polydipsia (PU/PD), decreased renal concentrating ability, azotemia and signs of clinical illness.[21-24] This effect was not consistent in all patients. Return of normal renal function in affected patients often required several weeks or months. The nephrotoxicosis is thought to be mediated through liberation of inorganic fluoride ions during metabolism of methoxyflurane[22], and is directly related to the magnitude of exposure to methoxyflurane (depth and duration of the anesthesia).[22] Histopathologic examination of kidneys from patients with methoxyflurane nephrotoxicity revealed nonspecific renal tubular degeneration, interstitial fibrosis, increased numbers of inflammatory cells in the interstitium and, sometimes, sheets of calcium oxalate crystals within and surrounding the renal tubules.[21,24]

Several studies have attempted to produce methoxyflurane nephrotoxicosis in the dog.[17-20] Although the serum inorganic fluoride levels reported in the dogs in these studies were equal to or higher than those associated with toxicity in humans, no clinical, clinicopathologic, or histopathologic evidence of overt renal toxicity was documented.[18,19] All of the studies, however, did note a transient PU/PD following anesthesia. No evaluation of renal concentrating ability (water deprivation or ADH stimulation) was performed to determine if the PU/PD resulted from an inability of the kidney to conserve water or a primary polydipsia. This polyuria could

represent a milder form of the toxicity seen in humans, however, it is more likely that it is due to an effect of methoxyflurane itself rather than a toxic effect of its metabolites. This is suggested by the inhibition of vasopressin stimulated water transport seen during methoxyflurane exposure in the in vitro studies using toad urinary bladders.[10,28] Levine points out that it is unlikely that bladder epithelial cells possess the enzyme systems necessary to metabolize methoxyflurane to fluoride, furthermore, response of the toad bladder epithelium to fluoride exposure is different than the response to methoxyflurane exposure. He concluded that it was unlikely that accumulation of fluoride played any role in the effects seen in his study.[28] If this is true, it is likely that methoxyflurane may cause a renal concentrating defect in the mammalian kidney that is distinct from the nephrotoxicosis caused by accumulation of its metabolites.

The results of this study indicate that methoxyflurane anesthesia results in both decreased renal concentrating ability and decreased free water clearance. The decrease in renal concentrating ability could be associated with either decreased affinity of ADH for receptors on the renal collecting ducts, decreased responsiveness of the renal collecting ducts following ADH binding to receptors, or decreased renal medullary osmolality. The decreased free water clearance appears to result from stimulation of endogenous ADH release. The magnitude of the decrease in renal concentrating ability is sufficient to impair accurate evaluation of renal function during and immediately following anesthesia.

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