**Methohexital Impairs Osmoregulation**

*Studies in Conscious and Anesthetized Volume-expanded Dogs*

Mailei Kasner, M.D.,* Jochen Große,* Martin Krebs, M.D.,* Gabriele Kaczmarczyk, M.D.†

**Background:** Anesthetic agents influence central regulations. This study investigated the effects of methohexital anesthesia on renal and hormonal responses to acute sodium and water loading in dogs in the absence of surgical stress.

**Methods:** Fourteen experiments were performed in seven well-trained, chronically tracheotomized beagle dogs kept in highly standardized environmental and dietary conditions (2.5 mmol sodium and 91 ml water/kg body weight daily). Experiments lasted 3 h, while the dogs were conscious (7 experiments) or, after 1 h control, while they were anesthetized (7 experiments) with methohexital (initial dose 6.6 mg/kg body weight and maintenance infusion 0.34 mg·min⁻¹·kg⁻¹ body weight) over a period of 2 h. In both experiments, extracellular volume expansion was performed by intravenous infusion of a balanced isosmolar electrolyte solution (0.5 ml·min⁻¹·kg⁻¹ body weight). Normal arterial blood gases were maintained by controlled mechanical ventilation. In another five dogs the same protocol was used, and vasopressin (0.05 μU·min⁻¹·kg⁻¹ body weight) was infused intravenously during methohexital anesthesia.

**Results:** Values are given as means. During methohexital anesthesia, mean arterial pressure decreased from 108 to 101 mmHg, and heart rate increased from 95 to 146 beats/min. Renal sodium excretion decreased; urine volume increased; and urine osmolality decreased from 235 to 155 mosm/L, whereas plasma osmolality increased from 301 to 312 mosm/L because of an increase in plasma sodium concentration from 148 to 154 mmol/L. Plasma renin activity, plasma aldosterone concentration, plasma atrial natriuretic peptide, and plasma antidiuretic hormone concentrations (range 1.8–2.8 pg/ml) did not change in either protocol. In the presence of exogenous vasopressin (anti-diuretic hormone 3.3 pg/ml), water diuresis did not occur, and neither plasma osmolality nor the plasma concentration of sodium changed.

**Conclusions:** Methohexital may impair osmoregulation by inhibiting adequate pituitary antidiuretic hormone release in response to an osmotic challenge. (Key words: Anesthetics, intravenous: methohexital. Hormones: renin–angiotensin–aldosterone system. Kidney(s), renal function: water diuresis. Osmoregulation: antidiuretic hormone.)

ANESTHETIC agents are known to impair regulation of body fluid homeostasis. Many studies in humans and experimental animals have shown that general anesthesia reduces urine volume and sodium excretion (U_aNa,V). Barbiturates are widely used for sedation and anesthesia. Their antidiuretic effects, described by DeBodo and Prescott in 1945, have been documented repeatedly. However, studies investigating the effects of anesthetics alone (without the complicating influence of surgical stress) are rare and results differ from those during clinical anesthesia. For example, a study in monkeys demonstrated an increase in renal U_aNa,V in response to pentobarbital anesthesia when compared with the conscious state, and a study in dogs demonstrated an increase in urine volume and renal U_aNa,V in response to thiopental anesthesia. In 1978, a study in our laboratory demonstrated water diuresis during methohexital anesthesia in dogs. However, values for plasma antidiuretic hormone (ADH) were not described in this study. In addition, changes in renal blood gas tensions, which are known to affect renal function, were possible in the spontaneously breathing anesthetized dogs of this study.

To explain these different findings and to extend our knowledge on the effects of a widely used anesthetic, we investigated the effects of the ultra–short-acting oxybarbiturate methohexital sodium on renal function and on hemodynamic and hormonal parameters in beagle dogs conscious or anesthetized in the absence of surgical stress. In addition, a third group of beagle dogs were anesthetized with methohexital in the presence of exogenous vasopressin.

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Materials and Methods

**Animals: Maintenance and Diet**

Twelve purebred female beagle dogs (mean body weight (body weight) 16.3 ± 1.2 kg) obtained from the Central Animal Laboratories of the Free University of Berlin were used. They were vaccinated and dewormed and had been selected from a stock of dogs according to their social behavior and tolerance of urinary bladder catheterization and gastric tube insertion. The dogs were kept in standardized conditions (21°C and 55% humidity), in a metabolic cage during the night and an animal room during the day; their general status, body temperature, and body weight were assessed daily. A prepared diet (supplemented with canned dog food during the first 4 or 5 postoperative days) was given daily at about 2 pm. If food intake was not completed spontaneously within 1 h, the remainder was given through a gastric tube. The diet (values per kilogram body weight per day) consisted of 58 g boiled rice, 12 g minced meat, and contained 277 kJ, water, potassium, and sodium were added to provide a total content of 91 ml water, 3.55 mmol potassium, and 2.5 mmol sodium. Body weight of each dog was constant over the whole time of the study.

The dogs had been previously trained to lie quietly on the animal table for at least 4 h. Permission to perform the experiments was obtained from the local Animal Care Committee (license of the Berlin government AZ.IV A 4-5855/17-46/89). Fourteen experiments were performed in seven dogs: two experiments (one control and one anesthetized) were done in each dog. In five other dogs, five experiments were performed.

**Anesthesia and Surgery**

Two operations were performed in each dog. General anesthesia was induced with 8 mg/kg body weight methohexitol (Brevimytil, Lilly, Giessen, Germany) intravenously and, after tracheal intubation, maintained with halothane (0.5–1.5%) and nitrous oxide and oxygen (2:1). In the first operation, the left common carotid artery was exteriorized in aseptic conditions (carotid loop). In the second operation, about 3 weeks later, tracheotomy was performed according to a method described elsewhere with minor modifications. Barking and breathing through the upper airway were not precluded between the experiments. Antibiotics (three injections of 0.5 g flucloxacillin and 80 mg gentamicin) were given intramuscularly on the day of tracheotomy and the following 2 days. After a 2–3-week recovery period, the dogs were accustomed to the insertion of an endotracheal tube (8–9 mm ID, Ultra Tracheoflex, Rüsch, Germany) and to controlled mechanical ventilation. One week before an experiment was performed, 150 ml venous blood was collected by foreleg vein puncture in each dog and was stored at 4°C (Biopack, Biotrans, Dreieich, Germany) for replacement of blood lost in the taking of plasma samples during the experiments. Intervals between two experiments in the same dog were at least 7 days.

**Experimental Protocol**

Experiments started at about 10 AM, 20 h after food intake. A self-retaining cather (16–20 Charmère, Norra, Beierdorf, Germany) was introduced into the urinary bladder. After insertion of an intravenous cannula (Braun-Müle, Braun, Melsungen, Germany) creatinine (Kreatinin, Merck, Darmstadt, Germany) was infused intravenously (priming dose 1.4 g dissolved in 50 ml 5% dextrose in water over a 30-min period and maintenance dose 0.14 g·h⁻¹). In aseptic conditions and local anesthesia, a double-lumen cather (Arrow-Howeis, Dahlhausen, Köln, Germany) was introduced into the right atrium via the superficial jugular vein. When typical right atrial pressure curves were obtained, the cather was withdrawn 2 cm and its position was assumed to be correct. The carotid loop was punctured in aseptic conditions (20-G cannula, Argyle, Medicut, Sherwood, Ireland) and connected to a pressure transducer (Viggo Spectramat, Spectramat, Bilthoven, The Netherlands). After insertion of the endotracheal tube and connection to the respirator (Servo 900 C, Solna, Sweden), the dogs were allowed to rest for 30 min. Two experiments (one control experiment and one methohexitol experiment) were performed in each of the seven dogs. In the five other dogs, an additional exogenous ADH infusion was applied during methohexitol anesthesia (table 1). Each experiment lasted 3 h.

In the 1st h, spontaneously breathing with 4 cmH₂O continuous positive airway pressure. In the 2nd and 3rd h, controlled mechanical ventilation with 10 cmH₂O positive end-expiratory pressure, either without (control) or with intravenous methohexitol (Brevimytil) infusion (initial dose 6.6 ± 0.7 mg·kg⁻¹ body weight = 10 ml fluid per dog and maintenance infusion 0.34 mg·min⁻¹·kg⁻¹ body weight = 30 ml fluid/h per dog). The amount of methohexitol was sufficient to suppress eyelash and pupillary reflexes. Osmolarity of the methohexitol solution was 359 mosm/l. In a third
protocol, exogenous vasopressin (Arg8-Vasopressin, Sigma Chemical, St. Louis, MO) was given intravenously at a dosage of 0.05 mU·min⁻¹·kg⁻¹ body weight during methohexital anesthesia.

A balanced electrolyte solution (content per liter 137 mmol sodium, 4 mmol potassium, 110 mmol chloride, 36.8 mmol acetate; Ionosteril, Fresenius, Bad Homburg, Germany) was given intravenously throughout the experiments with a roller pump (Infusomat II, Braun). The control group received 0.5 ml·min⁻¹·kg⁻¹ body weight (total amounts infused in 3 h per kilogram body weight: 90 ml water, 12.3 mmol sodium, and 0.36 mmol potassium). The methohexital group received 0.48 ml·min⁻¹·kg⁻¹ body weight (total amounts infused in 3 h per kilogram body weight: 86.4 ml water, 11.8 mmol sodium, and 0.35 mmol potassium, plus an additional 4.3 ml water and 0.8 mmol sodium because of the methohexital infusion).

The small difference in sodium intake between the two groups was attributable to the sodium content of the methohexital solution; anesthetized animals received 0.3 mmol/kg body weight more sodium (a 2.4% difference) than the conscious control animals.

Tidal volumes and respiratory frequencies were measured continuously. The trigger sensitivity of the respirator was set at −0.5 cmH₂O. Normoventilation was established and controlled by arterial blood gas analyses. Mean airway pressure was measured at the distal end of the endotracheal tube, mean arterial pressure (MAP), heart rate (HR), and changes in central venous pressure (CVP) were measured continuously (Spectramed transducers). All values were monitored (Dialogue 2000, Danica, Elmed, Denmark) and recorded every 20 s on-line (PC 40-III computer, Commodore, Braunschweig, Germany).

The urinary bladder was emptied completely (air washout) every 20 min to measure urine volume, creatinine, and U₆₀⁰V and potassium excretion (UₖV). Glomerular filtration rate (milliliters per minute) was calculated from according to the conventional clearance formula: creatinine clearance = renal creatinine excretion ÷ plasma creatinine concentration. Free-water clearance and fractional sodium excretion (FE₉₀⁰%) were calculated using standard formulas. The total amounts of water and sodium retained was calculated by the difference between the total amount of sodium and water infused during the observed time period and the amount of sodium and water excreted during the same time period. The retained amounts of sodium and water were added to the next time period.

At 20-min intervals 10-ml arterial blood samples were taken for the measurements of plasma osmolarity (P₉₀⁰), plasma creatinine concentration, plasma protein concentration (P₉₀⁰), hematocrit, plasma concentrations of sodium (P₉₀⁰) and of potassium (Pₖ), and blood gas analyses (ABL Radiometer, Copenhagen, Denmark). The blood samples were not replaced. At 60-min intervals 30-ml arterial blood samples were taken for measurements of ADH, atrial natriuretic peptide (ANP), aldosterone, and plasma renin activity (PRA). Each of the selected blood samples was replaced by 35 ml of the dog's own blood taken before the experiment (Pall Ultipur blood filter, Pall Biomedizien, Dreieich, Germany).

Sodium and potassium were measured by flame photometry (photometer, Eppendorf, Hamburg, Germany), creatinine by a modified Jaffé reaction (Analysator, Beckmann, Brea, CA), and osmolarity by freezing point depression (Osmometer, Roebling, Berlin, Germany). For ADH, PRA, aldosterone, and ANP measurements, blood was taken into precooled tubes prepared with sodium ethylenediamine tetracetic acid and were centrifuged at 4°C; the plasma was stored at −22°C until analysis. Commercially available radioimmunoassay kits were used to measure ANP (Henning, Berlin, Germany; intraassay coefficient of variation 11.5% and interassay coefficient of variation 14%), aldosterone (Aldoct-2, Sorin, Italy; intraassay coefficient of variation 12.7% and interassay coefficient of variation 12.4%), and PRA (New England Nuclear, North Billerica, MA; interassay coefficient of variation 13%).

Statistical Analysis

Statistical analysis was performed using the Cruncher Software program (Kaysville, Utah). Mann-Whitney U tests were used to compare continuously measured data from the seven dogs in the study with the six dogs in the control group. A value of p < 0.05 was considered to be statistically significant.

Results

**Hemodynamics**

HR, MAP, and CVP
1. All values are expressed as mean ± SEM. In the first 30 min after induction of anesthesia, the mean HR was 111 ± 5 bpm and the mean MAP was 86 ± 3 mm Hg in the control group and 110 ± 4 bpm and 85 ± 3 mm Hg in the methohexital group.

Renal Function

Urine volume
1. The average urine volume was 10 ± 2 ml/kg body weight during the first h. With increasing urine volumes in the control group, this was increased by a factor of 2.5.

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ica, MA; intraassay coefficient of variation 11% and interassay coefficient of variation 8.4%), expressed as nanograms of angiotensin I generated per hour of incubation per milliliter of plasma. ADH was measured with a commercially available radioimmunoassay kit (Biermann, Bad Nauheim, Germany) using a double-antibody separation technique after extraction. The standard range of the assay was 1.2–80.0 pg/ml, the sensitivity 0.6 pg/ml, and the intraassay coefficient of variability 8% at the middle sensitivity range.

At the end of the experiments infusions were stopped and all catheters removed. The tracheas were exstubated when the dogs were breathing spontaneously. After 1 h of observation the dogs were allowed to return to their home cages.

Statistical Analyses

Statistical analysis was performed by Number Cruncher Statistical Systems (version 5.1, J. L. Hintze, Kaysville, UT). Values are given as means ± SEM. The Mann-Whitney U test for paired variables was used to compare control and methohexital experiments in seven dogs and to compare the 1st h (conscious) with the 2nd and 3rd h (methohexital and vasopressin) in five dogs. A P value of less than 0.05 was considered to be statistically significant.

Results

Hemodynamics

HR, MAP, and changes in CVP are shown in figure 1. All values were similar in both groups during the 1st h. In the methohexital group HR increased by an average of 53 beats/min during the 2nd and 54 beats/min during the 3rd h when compared with that in the conscious control animals. MAP decreased by an average of 10 mmHg at the end of the 2nd h in the methohexital group in comparison with the control group. CVP did not change in either experimental protocol.

Renal Function

Urine volume, \( U_{\text{o},\text{V}} \), and \( \text{FE}_{\text{o},\text{Na}} \) are shown in figure 2. The values were similar in both groups during the 1st h. With ongoing extracellular volume expansion, urine volume, \( U_{\text{o},\text{V}} \), and \( \text{FE}_{\text{o},\text{Na}} \) increased in both groups. In the methohexital group, urine volume increased by an average of 95 \( \mu \text{l} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) body weight above the control values during the 2nd h. \( U_{\text{o},\text{V}} \) was decreased by an average of 6 \( \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) body weight during the 2nd and 11 \( \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) body weight during the 3rd h in the methohexital group when compared with the that in the conscious control group. In the methohexital group \( \text{FE}_{\text{o},\text{Na}} \) decreased by 0.8% during the 2nd, and by 1.2% during the 3rd h in comparison with the control group.

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Urine osmolarity ($U_{\text{osm}}$) is shown in figure 3. The values were similar in both experimental protocols during the 1st h. In the methohexitol-anesthetized animals $U_{\text{osm}}$ decreased during the 2nd and 3rd h when compared with those in the conscious control animals.

**Cumulative Balances of Water and Sodium**

The total amounts of water and sodium retained are listed in table 2. The values were similar during the 1st h. In the methohexitol group the amount of water retained was decreased whereas the amount of sodium retained was increased compared with that in the conscious control group.

**Hormonal Parameters**

PRA, ADH, aldosterone, and ANP values are provided in table 3. In the methohexitol group PRA was slightly increased during the 3rd h in comparison with the control group. ADH, aldosterone and ANP did not change throughout in either protocol.

**Plasma Values**

$P_{\text{Hb}}$, hematocrit, and $P_{\text{prox}}$ values are listed in table 4. The values were similar in both experimental protocols during the 1st h. In the methohexitol group $P_{\text{Hb}}$ decreased during the 2nd and 3rd h when compared with that in the conscious control group. Hematocrit and $P_{\text{prox}}$ decreased in both groups during the 2nd and 3rd h (not tested statistically).

$P_{\text{Na}}$ and $P_{\text{osm}}$ are shown in figure 3. The values were similar in both experimental protocols during the 1st h. In the methohexitol-anesthetized animals $P_{\text{Na}}$ and $P_{\text{osm}}$ increased during the 2nd and 3rd h when compared with those in the conscious control animals.

**Arterial Blood Gases**

Arterial oxygen tension, carbon dioxide tension, pH, and $HCO_3^-$ are listed in table 4. The values did not change throughout in either protocol.

**Airway Pressure**

Mean airway pressure ranged between 3 and 5 cmH$_2$O during the 1st h (4 cmH$_2$O continuous positive airway pressure) and increased during the 2nd and 3rd h (controlled mechanical ventilation with 10 cmH$_2$O positive end-expiratory pressure) to values between 9 and 12 cmH$_2$O in both experimental protocols.

**Vasopressin Experiments**

Values for HR, MAP, change in CVP, ADH, $P_{\text{osm}}$, $P_{\text{Na}}$, urine volume, and $U_{\text{osm}}$ of the five dogs treated

Fig. 2. Urine volume (V), sodium excretion ($U_{\text{Na}}$V), and fractional sodium excretion (F$_{\text{Na}}$,%) during the 1st h (conscious) and the 2nd and 3rd h in animals while conscious (control experiments) (open symbols) or while anesthetized with methohexitol (closed symbols). Values are means ± SEM, n = 7. *P < 0.05 versus control experiments.

Values for glomerular filtration rate, free-water clearance, and $U_{\text{Na}}$V are listed in table 2. The values were similar in both experimental protocols during the 1st h. In the methohexitol-anesthetized animals free-water clearance was increased during the 2nd and 3rd h when compared with that in the conscious control animals. Glomerular filtration rate and $U_{\text{Na}}$V increased in the conscious control group and were decreased during the 3rd h in the methohexitol group in comparison with the control group.
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Table 2. Effects of Methohexital Anesthesia on Glomerular Filtration Rate (GFR), Free Water Clearance (C_{\text{fwater}}), Osmolar Clearance (C_{\text{osmol}}), Cumulative Balance of Water (Cum_{\text{water}}) and Sodium (Cum_{\text{na}}), and Potassium Excretion (U_{\text{kV}}) during Extracellular Volume Expansion

<table>
<thead>
<tr>
<th></th>
<th>Hour 1 (CPAP 4)</th>
<th>Hour 2 (CMV 10)</th>
<th>Hour 3 (CMV 10)</th>
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<tr>
<td></td>
<td>Concns</td>
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<tr>
<td>GFR (ml·min^{-1}·kg^{-1})</td>
<td>4.1 ± 0.2</td>
<td>4.4 ± 0.3</td>
<td>4.8 ± 0.3</td>
</tr>
<tr>
<td>Methohexital</td>
<td>4.0 ± 0.1</td>
<td>4.1 ± 0.1</td>
<td>4.1 ± 0.1*</td>
</tr>
<tr>
<td>C_{\text{fwater}} (µl·min^{-1}·kg^{-1})</td>
<td>50.6 ± 12.3</td>
<td>15 ± 7.1</td>
<td>28.1 ± 10.1</td>
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<td>40.6 ± 14.5</td>
<td>163.9 ± 23.2*</td>
<td>226.8 ± 37.1*</td>
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<tr>
<td>Cum_{\text{water}} (µl/kg)</td>
<td>17.8 ± 1.6</td>
<td>30.7 ± 3.9</td>
<td>37.7 ± 6.8</td>
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<tr>
<td>Methohexital</td>
<td>17.8 ± 2.2</td>
<td>24.9 ± 5.3</td>
<td>28.0 ± 5.7*</td>
</tr>
<tr>
<td>C_{\text{osmol}} (µl·min^{-1}·kg^{-1})</td>
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<td>0.35 ± 0.02</td>
</tr>
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<td>0.21 ± 0.02</td>
<td>0.22 ± 0.02*</td>
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<tr>
<td>Cum_{\text{na}} (mmol/kg)</td>
<td>3.5 ± 0.2</td>
<td>6.0 ± 0.4</td>
<td>7.8 ± 0.6</td>
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<td>3.5 ± 0.2</td>
<td>6.4 ± 0.5</td>
<td>8.9 ± 0.7*</td>
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<tr>
<td>U_{\text{kV}} (µmol·min^{-1}·kg^{-1})</td>
<td>2.0 ± 0.2</td>
<td>3.4 ± 0.3</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>Methohexital</td>
<td>2.2 ± 0.2</td>
<td>2.5 ± 0.3</td>
<td>2.0 ± 0.3*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM, n = 7.
* P < 0.05 versus control.

with methohexital and vasopressin infusion are provided in table 5. HR increased during the 2nd and 3rd h. MAP and CVP did not change. ADH, U_{\text{osmol}} and U_{\text{kV}} increased during the 2nd and 3rd h. P_{\text{osmol}} decreased. P_{\text{osmol}} and urine volume did not change throughout the protocol.

Discussion

The current study was performed in highly standardized conditions in conscious and anesthetized dogs to investigate the effects of methohexital on the homeostatic control of sodium and water balance. In contrast to other studies, we provided a standardized sodium and water supply and omitted surgical stress and blood gas changes in relation to anesthesia by controlled mechanical ventilation. The results demonstrate the occurrence of a striking dissociation between an increase in P_{\text{osmol}} and a decrease in U_{\text{osmol}} in the presence of unchanged plasma ADH concentrations during methohexital anesthesia. Apparently, central osmoregulation is impaired by this widely used barbiturate, whereas the renal response to exogenous vasopressin is unimpaired.

An increase in P_{\text{osmol}} is one of the most powerful stimuli to ADH release, as has been known since the pioneering investigations by Verney in 1947.9 These relations have been described repeatedly in various species, including rats10 and dogs.11 A threefold increase in plasma ADH concentration caused by an increase in P_{\text{osmol}} by 9 mosm/l was described in chloralose–pentobarbital–anesthetized dogs.11 In the current study P_{\text{osmol}} increased by an average of 11 mosm/l without a change in plasma ADH concentration (fig. 3 and table 3). The reason for the discrepancy between the current and the earlier study11 is not clear. It is possible that extracellular volume expansion, done in the current study and not performed in the other,11 attenuated the central response to an osmotic stimulus. Although CVP did not change, extracellular volume expansion is documented by the increase in body sodium and water (calculation of cumulative sodium and water balance). In addition, hematocrit and P_{\text{osmol}} decreased because of hemodilution (not tested statistically). The conscious animals retained an amount of 38 ml water/kg body weight (corresponding to about 18% of extracellular fluid volume) and the anesthetized dogs retained 28 ml water/kg body weight (about 14% of extracellular fluid volume). However, the dogs’ lungs in the current study were
between the study in chloralose—pentobarbital—anesthetized dogs and the current study in methohexital—anesthetized dogs is that chloralose, known to maintain central reflex activity, maintains—even in combination with pentobarbital—central sensitivity to osmotic stimuli whereas methohexital, in the current study, did not.

Studies comparing volume and osmotic stimuli on ADH release in dogs kept in high-volume conditions are not available. However, in rats a much higher sensitivity of the pituitary to osmotic stimuli than to volume changes was demonstrated. In healthy adults in varying states of hydration the relation between an increase in P_{osm} and ADH release was described as a linear regression function demonstrating a prompt increase in ADH above a threshold of 280 mosm/kg. In contrast, in our study P_{osm} increased to an average of 312 mosm/kg without any changes in plasma ADH. Also, in the methohexital group, MAP decreased by 7 mmHg. This MAP decrease should amplify the osmotic signal to the hypothalamic-hypophyseal ADH release mechanism. In the presence of exogenous vasopressin MAP decrease did not occur as expected. Despite the extracellular volume expansion CVP did not change in either protocol. Thus a possible inhibition of ADH release originating from low-pressure volume receptors can be ruled out.

However, it cannot be discerned whether methohexital induced a shift of the osmotic threshold to

Fig. 3. Plasma osmolarity (P_{osm}), urine osmolarity (U_{osm}), and plasma sodium concentration (P_{Na}) during the 1st h (conscious) and the 2nd and 3rd h in animals while conscious (control experiments) (open symbols) or while anesthetized with methohexital (closed symbols). Values are means ± SEM, n = 7. *P < 0.05 versus control experiments.

ventilated mechanically (to avoid changes in renal hemodynamics resulting from changes in arterial carbon dioxide tension) with an increase in mean airway pressure by about 6 cmH_{2}O, and it is likely that atrial transmural pressures, which were not measured, may have decreased by 2–4 cmH_{2}O. Thus, although extracellular fluid volume was expanded, it is uncertain whether an inhibitory influence on ADH release was present. Another explanation for the discrepancy between the study in chloralose—pentobarbital—anesthetized dogs and the current study in methohexital—anesthetized dogs is that chloralose, known to maintain central reflex activity, maintains—even in combination with pentobarbital—central sensitivity to osmotic stimuli whereas methohexital, in the current study, did not.

Table 3. Effects of Methohexital Anesthesia on Plasma Renin Activity (PRA), Plasma Antidiuretic Hormone Concentration (ADH), Plasma Aldosterone Concentration (ALDO), and Plasma Atrial Natriuretic Peptide Concentration (ANP) during Extracellular Volume Expansion

<table>
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<th></th>
<th>Hour 1 (CPAP 4)</th>
<th>Hour 2 (CPAP 10)</th>
<th>Hour 3 (CPAP 10)</th>
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<td>PRA (ng ANGI·ml⁻¹·h⁻¹)</td>
<td></td>
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<tr>
<td>Control</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.5 ± 0.2</td>
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<tr>
<td>Methohexital</td>
<td>1.5 ± 0.6</td>
<td>1.8 ± 0.6</td>
<td>1.1 ± 0.2</td>
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<tr>
<td>ADH (pg/ml)</td>
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<tr>
<td>Control</td>
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<td>2.3 ± 0.8</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>Methohexital</td>
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<tr>
<td>ALDO (pg/ml)</td>
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<tr>
<td>Control</td>
<td>37 ± 9</td>
<td>34 ± 7</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Methohexital</td>
<td>33 ± 7</td>
<td>32 ± 4</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
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<tr>
<td>Control</td>
<td>66 ± 10</td>
<td>67 ± 17</td>
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<tr>
<td>Methohexital</td>
<td>60 ± 7</td>
<td>57 ± 7</td>
<td>54 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± SEM, n = 7. *P < 0.05 versus control.
METHOHEXITAL IMPAIRS OSMOREGULATION

Table 4. Effects of Methohexital Anesthesia on Plasma Potassium Concentration (P_{k}), Hematocrit (Hct), Plasma Protein Concentration (P_{pro}), Arterial Blood Gases (P_{aco2}, P_{aco3}), pH, and HCO_{3} during Extracellular Volume Expansion

| Table 4. Effects of Methohexital Anesthesia on Plasma Potassium Concentration (P_{k}), Hematocrit (Hct), Plasma Protein Concentration (P_{pro}), Arterial Blood Gases (P_{aco2}, P_{aco3}), pH, and HCO_{3} during Extracellular Volume Expansion
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>P_{k} (mmol/l)</td>
<td>Control</td>
<td>Methohexital</td>
<td>Control</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>3.6 ± 0.02</td>
<td>3.5 ± 0.03</td>
<td>3.5 ± 0.01</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>35 ± 2</td>
<td>32 ± 2</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>P_{aco2} (mmHg)</td>
<td>99 ± 3</td>
<td>100 ± 2</td>
<td>101 ± 3</td>
</tr>
<tr>
<td>P_{aco3} (mmHg)</td>
<td>102 ± 4</td>
<td>102 ± 3</td>
<td>101 ± 2</td>
</tr>
<tr>
<td>Control</td>
<td>7.40 ± 0.01</td>
<td>7.39 ± 0.01</td>
<td>7.42 ± 0.01</td>
</tr>
<tr>
<td>Methohexital</td>
<td>7.38 ± 0.01</td>
<td>7.40 ± 0.01</td>
<td>7.40 ± 0.01</td>
</tr>
<tr>
<td>pH</td>
<td>23.4 ± 0.3</td>
<td>22.8 ± 0.2</td>
<td>24.2 ± 0.3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM, n = 7.

* P < 0.05 versus control.

In the methohexital group, the increase in P_{k} from 301 to 312 mosm/kg was caused by an increase in P_{aco2} from 148 to 154 mm. The increase in P_{k} is the result of the increase in urine volume in relation to the decrease in renal U_{Na}V. This can be con-

higher osmolarities or inhibited ADH release completely. Two events in response to methohexital anesthesia in conditions of isotonic volume loading should be distinguished: the first event is an increase in free-water clearance caused by a reduction in U_{Na}V and an increase in urinary flow causing P_{k} and P_{aco2} to increase. This initial response results from methohexital anesthesia. The second event, the impaired response of plasma ADH to the increase in P_{k}, could be attributed to an inhibition of ADH release by methohexital itself. However, an impaired ADH release also can be caused by the initial effect of methohexital on renal reabsorption. The experiments with intravenous exogenous vasopressin were performed to determine whether central ADH release was disturbed in the methohexital group or whether the kidney did not respond to the increase in plasma ADH concentrations, which were eventually too small for detection by the assay used. The results of these vasopressin experiments demonstrate that exogenous vasopressin prevented an increase in P_{k}.

These findings agree with earlier investigations of our laboratory demonstrating that exogenous vasopressin inhibited the water diuresis during methohexital anesthesia. However, a delineation of involved mechanisms is not possible with the used study design. Therefore the presence of a nephrogenic diabetes insipidus-like syndrome in conditions of a methohexital-induced osmotic challenge, although not very likely, can not be excluded completely.

The effects of ADH infusion on plasma ADH concentrations and renal concentrating ability have been investigated in a study in conscious dogs. The results of those experiments led to the suggestion that even subpicomolar changes in plasma ADH in a calculated range of 0.05–0.13 pg/ml increased U_{Na}V and decreased free-water clearance. The authors of that study missed such small increases in plasma ADH by their measurement technique. The same may be true for the current study: the sensitivity of our assay is not sufficient to detect such small changes in ADH. However, in the current study free-water clearance increased, osmolar clearance decreased, and water diuresis occurred during methohexital anesthesia.

In the methohexital group of the current study, the increase in P_{k} from 301 to 312 mosm/kg was caused by an increase in P_{aco2} from 148 to 154 mm. The increase in P_{k} is the result of the increase in urine volume in relation to the decrease in renal U_{Na}V. This can be con-

| Table 5. Effects of Methohexital Anesthesia on Heart Rate (HR), Mean Arterial Blood Pressure (MAP), Changes of Central Venous Pressure (ΔCVP), Plasma Antidiuretic Hormone Concentration (ADH), Plasma Osmolarity (P_{osm}), Urine Osmolarity (U_{osm}), Plasma Sodium Concentration (P_{Na}), Urine Volume (V), and Sodium Excretion (U_{Na}V) in the Presence of Exogenous Vasopressin (0.05 mU·min^{-1}·kg^{-1} body weight)
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<tr>
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</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>Control</td>
<td>Methohexital + Vasopressin</td>
<td>Control</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>105 ± 3</td>
<td>136 ± 5*</td>
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<tr>
<td>116 ± 2</td>
<td>115 ± 3</td>
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<tr>
<td>0.6 ± 0.4*</td>
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<tr>
<td>1.1 ± 0.1</td>
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</tr>
<tr>
<td>33.3 ± 0.2*</td>
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</tr>
<tr>
<td>304 ± 1</td>
<td>300 ± 1*</td>
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</tr>
<tr>
<td>238 ± 53</td>
<td>420 ± 23*</td>
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</tr>
<tr>
<td>151 ± 1</td>
<td>150 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.2 ± 2</td>
<td>37 ± 3*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM, n = 4.

* P < 0.05 versus Hour 1.

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cluded from the following estimation: with the assumption that the sodium distribution space is greater than 20.6% of body weight, a value measured as insulin space in dogs, it can be calculated that the measured PaNa in the methohexitol group of the current study is close to values that can be calculated taking into account the amount of sodium and water retained.

In the current study, UaNa decreased during methohexitol anesthesia. This decrease in renal UaNa, when compared with the conscious control state, was on one hand caused by a decrease in FENa, (fig. 2). On the other hand, glomerular filtration rate, which increased in the control experiments in response to extracellular volume expansion, did not change in the methohexitol experiments. The lack of change in glomerular filtration rate and the increase in tubular sodium reabsorption most likely result from an increase in renal sympathetic nerve activity. The greater sympathetic activity in the methohexitol group is documented by an increase in HR (fig. 1), which can also be found in the vasopressin experiments (table 5). The decrease in PaNa and UaNa, which can be most likely explained by a potassium shift from the extracellular to the intracellular space, most likely indicates high sympathetic activity. In so far it is surprising that only small changes in PRA were observed, and, in addition, urine volume increased although MAP decreased by 7 mmHg during methohexitol anesthesia.

The increase in HR during methohexitol anesthesia is one of the well-known effects of barbiturates. It was suggested that renal sympathetic nerve activity however was depressed by thiopental anesthesia leading to a decrease in tubular sodium reabsorption not observed in the current study (fig. 2). It may be that thiopental acts different from the oxybarbiturate methohexitol and/or the experimental conditions before the experiments may play a role.

In the current study plasma aldosterone concentrations did not change. This finding agrees with the results of a study in humans in which no changes in aldosterone occurred during methohexitol anesthesia. Apparently the increase in extracellular volume and PaNa suppressed aldosterone release in our study. Plasma ANP concentrations did not change. As the extracellular volume increased and the atrial transmural pressures most likely decreased because of mechanical ventilation, these opposite stimuli on ANP release may have antagonized each other, as seen previously.

It also seems unlikely that methohexitol induced a nephrogenic diabetes insipidus-like syndrome, because exogenous application of ADH has been demonstrated to increase UaNa and, in the current study, plasma ADH concentrations remained low in the presence of an increased PaNa. The intravenous vasopressin experiments, which were performed to corroborate earlier results, clearly confirmed that exogenous vasopressin prevented the occurrence of water diuresis during methohexitol anesthesia. Renal response to vasopressin was not impaired. Therefore, we conclude that methohexitol interferes with central osmoregulation.

In summary, this study investigated the homeostatic responses to acute sodium and water loading in dogs during methohexitol anesthesia without the complicating influences of surgical stress. Despite an increase in PaNa caused by an increase in PaNa and a decrease in UaNa, plasma ADH concentration did not increase in the presence of an unchanged CVP. The administration of exogenous vasopressin in the presence of methohexitol anesthesia prevented water diuresis. We conclude that methohexitol impairs central osmoregulation.

The authors thank Birgit Brandt for excellent technical assistance and Hassan Salak for taking care of the dogs.

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