THE ANTIDIURETIC EFFECTS OF ANESTHETIC AGENTS* †‡§

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The effects of anesthetics upon renal function have been observed by clinicians and laboratory investigators since the turn of the century (1). The knowledge of the basic mechanisms of these effects, and indeed of many of the alterations themselves, have remained obscure. Observed changes in renal function during general anesthesia (fig. 1) have been attributed to changes in systemic circulation (2); to local action of anesthetic drugs on renal parenchyma or renal vessels (3, 4); to acidosis during anesthesia for which the kidney must compensate; and to adrenal cortical stimulation which influences the reabsorption of sodium and potassium (5, 6). We have been most interested in the effects of the anesthetic drugs upon the excretion of water, ordinarily under the control of the posterior pituitary by its antidiuretic hormone.

Earlier workers have observed an antidiuretic effect with various central nervous system depressants (7, 8, 9). DeBodo has observed an antidiuretic effect after morphine, phenobarbital, and pentobarbital, and has presented evidence that this effect is mediated through the production of antidiuretic hormone by the posterior pituitary. Silvette (10) observed an antidiuretic effect after thiopental in rats and concluded it was not mediated by the posterior pituitary. The validity of his conclusions has been questioned by DeBodo (9). Handley (11) observed an antidiuretic effect after morphine and showed some data indicating that this antidiuretic effect might be caused both by the production of antidiuretic hormone and by direct action on renal blood vessels.

We have endeavored to study, under carefully controlled conditions in the dog, the antidiuretic effects of various commonly used anesthetics.

METHODS

Mongrel female dogs were used throughout all experiments.|| These dogs were perineotomized to facilitate bladder catheterization. All

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† This investigation was supported by a grant from Burroughs Wellcome & Co.
‡ Read before the annual meeting of the American Society of Anesthesiologists, Inc., Cincinnati, Ohio, October 25, 1954.
§ Accepted for publication February 8, 1955.
|| All of the dogs used in this study were trained to accept intravenous puncture, stomach intubation and bladder catheterization without struggling or excitement.

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of the animals were twenty hours postprandial at the time of the experiment. Four hours before each experiment the animals were hydrated by stomach tube with 20 cc. of tap water per kilogram of body weight. At the beginning of each experiment another 20 cc. of tap water per kilogram was given. Under the above conditions, the response of the normal hydrated dogs to 20 cc. of water per kilogram is relatively constant (fig. 2). It has also been observed that this amount of water will be absorbed from the dog's gastrointestinal tract within thirty minutes (8). Every fifteen minutes the bladder was emptied through an indwelling catheter and the urine volume was measured. Usually within thirty minutes a water diuresis was established and the animals were then subjected to the various anesthetic drugs.

An endotracheal tube was inserted under light thiopental anesthesia prior to giving the anesthetic drugs to be tested in order to insure adequate gas exchange and to avoid excitement, which would cause antidiuresis.

**Thiopental.** Thiopental, even in very large doses (enough to cause full surgical anesthesia for one hour), failed to produce an antidiuretic

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**Fig. 1.** Renal function during surgery.
"TAFFY" 15 KILOS
20 cc/KILO WATER GIVEN
BY STOMACH TUBE AT
POINT O.

Fig. 2. Response of dogs to hydrations.

"TAFFY" 15 KILOS
20 cc/KILO WATER GIVEN
BY STOMACH TUBE AT
POINT O.
↓ 6 cc. PENT. I.V.
↓ 10 cc. PENT. I.V.
↓ 400 mg. TOTAL PENTOTHAL

Fig. 3. Response to thiopental anesthesia.
effect under the conditions of this experiment (12 experiments on 2 dogs) (fig. 3). It therefore appeared feasible to use thiopental for endotracheal intubation and for the induction of inhalational anesthesia without an excitement stage.

*Ether.* Ether anesthesia, induced after thiopental, by the closed inhalational technique produced an antidiuretic effect in 10 experiments on 2 dogs (fig. 4). It was noted that the strength of the antidiuretic effect seemed to vary with the depth of anesthesia. Very little excretion occurred in the deep planes of anesthesia, and relatively more excretion occurred as the anesthesia grew lighter.

![Figure 4. Antidiuretic effects of ether.](image)

In order to observe how long after ether anesthesia the antidiuretic effect could persist, the dogs were subjected to three hours of ether anesthesia. As soon as the dogs could stand on their feet (about thirty minutes after ether inhalation ceased), 20 cc. of water per kilogram of weight was given. A normal diuretic response occurred (fig. 5).

*Cyclopropane.* The experiments with cyclopropane were done in the same manner as with ether. Here the results at first were not as clear. While on most occasions (7 times in 10 experiments on 4 dogs) an antidiuretic effect was observed, it was absent or seemingly transient on others. As our experience with handling this drug in dogs in-
creased, we were able to repeat our results constantly and to observe an antidiuretic effect. (8 experiments on the same 4 dogs) (fig. 6). The antidiuretic effect required deep planes of anesthesia and disappeared very rapidly as anesthesia lightened.

Morphine and Pentobarbital. It was decided to repeat the work of DeBodo (7, 8, 9) with morphine and pentobarbital because the conditions of our experiment were somewhat different. A strong antidiuretic curve was observed after 2.5 mg. of morphine per kilogram was given to the normal dog (3 experiments on 2 dogs). In order to rule out hypoxia as a cause of this antidiuresis, the dogs were first

given thiopental, intubated, and then ventilated with pure oxygen before and after the administration of morphine (fig. 7). The same strong antidiuretic effect was observed.

DeBodo found that pentobarbital caused an antidiuretic effect in dogs. In our experiments a typical antidiuretic curve could not be elicited with pentobarbital in experiments on 5 dogs. However, the total water excreted was less after pentobarbital than in the normal dogs. DeBodo also found that this effect could be abolished by section of the pituitary stalk and section of the hypothalamic-pituitary tract.

Antidiuretic effects following section of pulmonary stalk and Hypo-
thalamic Tract. The antidiuretic effects that were demonstrated in normal dogs might be caused by stimulation of antidiuretic hormone or by direct effect of the anesthetic agent upon the kidney. In order further to investigate the possibility of antidiuretic hormone release, 6 of the same dogs used for the preceding experiments were subjected to high pituitary stalk and hypothalamic tract section by the oral approach. Within thirty days 4 of the animals had severe "diabetes insipidus." They excreted from 3,500 to 6,000 cc. of urine per twenty-four hours. Some investigators used the appearance of a sustained diuresis and polydypsia as a criterion of the adequate destruction of

post-pituitary tissue (8, 9). However, there are several extremely potent stimulators of posterior pituitary tissue that will evoke an antidiuretic effect in animals after pituitary stalk section and the onset of diuresis, with the inference that there is some remnant of pituitary tissue left. (12) The dogs with "diabetes insipidus" used in this study were only those animals which showed no response, or only a highly questionable response, to 3-hydroxy-phenyl-cinchoninic acid. We obtained 3 such dogs. In these animals the same strong antidiuretic effect was observed after ether (fig. 8) (3 experiments on 3 dogs). Again this seemed to vary with depth of anesthesia.

"TAFY" 14.8 KILOS
20cc./KILO WATER GIVEN
BY STOMACH TUBE AT
POINT 0
↓ 12 cc. PENT. I.V.
↓ CYCLO INHALATION BEGUN
↓ CYCLO INHALATION STOPPED

Fig. 6. Antidiuretic effects of cyclopropane.
Fig. 7. Antidiuretic effects of morphine.

"SUE" 13.4 KILOS
20 cc./KILO WATER GIVEN
BY STOMACH TUBE AT
POINT 0.

↓ 10 cc. PENT. I.V. (INTUBATION
and 100% OXYGEN
ADMINISTERED)

↓ 32 mg. MORPHINE SULFATE

Fig. 8. Antidiuretic effects in dogs with "diabetes insipidus" following ether.

"TAFFY" 18 KILOS
20 cc./KILO WATER GIVEN
BY STOMACH TUBE AT
POINT 0.

↓ 13 cc. PENT. I.V.
ETHER INHALATION BEGUN
ETHER INHALATION STOPPED
With cyclopropane, the antidiuretic effect was observed in the "diabetes insipidus" dogs as in the normal animals (3 experiments on 3 dogs) (fig. 9).

With morphine the antidiuretic effect was elicited in 2 dogs after the production of "diabetes insipidus" as before. In one animal, the antidiuretic response to 2.5 mg. of morphine per kilogram was present although it appeared modified (fig. 10).

With pentobarbital, 30 mg. per kilogram, an antidiuretic curve was observed with all of the "diabetes insipidus" animals. The effect was over quickly and the total water excretion was more in the "diabetes insipidus" animals than in the normal animals (fig. 11).

Fig. 9. Antidiuretic effects following cyclopropane in normal dogs and dogs with "diabetes insipidus."

"SALLY" 14.5 KILOS (DIABETES INSIPIDUS)
20 cc/KILO WATER GIVEN
BY STOMACH TUBE AT
POINT 0.

1. 12 cc PENT. I.V
2. CYCLO INHALATION BEGUN
3. CYCLO INHALATION STOPPED

COMMENT

It seems clear to us that some anesthetic agents, particularly ether, cyclopropane, morphine and possibly pentobarbital, exert an antidiuretic effect. It is felt that evidence is presented here that this effect is not persistent after the central nervous system depression of the drugs has passed, and that it is not mediated through the posterior pituitary. Possibly this antidiuretic effect is caused by a marked decrease in renal blood flow which these drugs directly or indirectly may cause. Brewster and Isaacs (13) have recently estimated that epineph-
The urine is liberated at a rate of 1 microgram per kilogram per hour during ether anesthesia in dogs. It is possible that the antidiuretic effect of ether is caused by ephinephrine.

Lequesne and Harris (6) in England have shown, as Moyer (14) and others had demonstrated previously, that surgical patients may have a persistent antidiuresis postoperatively and that this persistent antidiuresis may lead in some cases to postoperative water retention. Eisen (15) showed that an antidiuretic hormone-like substance can be detected in a patient’s urine for as long as twenty-four hours postoperatively.

"SPOT" 21 KILOS
(DIABETES INSIPIDUS)
20 cc/KILO WATER GIVEN
BY STOMACH TUBE AT
POINT 0
↓ 2.5 mg/KILO MORPHINE
SULFATE

Fig. 10. Antidiuretic response following morphine.

Our evidence does not support the hypothesis that anesthetic drugs themselves may be responsible for such a prolonged antidiuretic effect. Perhaps the surgical operation itself adds the stimulus for a persistent antidiuresis. Finally, it has been observed that the antidiuresis caused by anesthetic drugs seems to be related to the depth of anesthesia.

Summary
1. A group of normal dogs were subjected to thiopental, ether, cyclopropane, pentobarbital and morphine anesthesia during water
"TAFFY" 18 KILOS
(DIABETES INSIPIDUS)
20 cc./Kilo WATER GIVEN
BY STOMACH TUBE AT
POINT 0
↓ 30mg/Kilo PENTOBARBITAL

Fig. 11. Antidiuretic response following pentobarbital after
production of "diabetes insipidus."]

diuresis. No antidiuretic effect was observed with thiopental, whereas
a modified antidiuretic effect was observed with pentobarbital. Ether,
cyclopropane, and morphine showed a marked antidiuretic effect.

2. The same dogs were then subjected to high pituitary stalk and
hypothalamic-pituitary tract section. After the onset of "diabetes
insipidus" the animals were again subjected to ether, cyclopropane,
pentobarbital and morphine anesthesia during water diuresis. Anti-
diuretic effects were still noted in these dogs with ether, cyclopropane,
morphine and pentobarbital.

ACKNOWLEDGMENT

The author wishes to express his appreciation to Dr. E. H. Dearborn of Boston University
for performing the high pituitary stalk section and hypothalamic pituitary tract section in
these animals.

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