Effects of Intravenous Veratridine on Plasma Antidiuretic Hormone Concentration and Renal Function in Dogs[1] (36513)

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Thomas recently reported that the iv injection of veratridine into dogs produced an increase in urine flow (1). Since veratridine is known to stimulate ventricular, atrial, and pulmonary receptors (2), Thomas (1) suggested that the diuresis was reflexly induced by stimulation of veratridine-sensitive cardiopulmonary receptors. She surmised that atrial type B receptors, which have been implicated in blood volume control (3), were involved, and she concluded that her results supported the concept that atrial receptors play a role in fluid volume regulation. In a recent review, Gauer, Henry and Behn (3) suggested that the increase in urine flow in Thomas's studies, which took 20–30 min to peak, might be produced by a decrease in circulating antidiuretic hormone (ADH).

These suggestions, based on rather indirect evidence, prompted us to evaluate the effect of iv veratridine on plasma ADH concentration and renal function. Our results demonstrate that plasma ADH is not decreased by veratridine. On the contrary, ADH levels are elevated significantly 5 min after veratridine is given. Urine flow measurements did not confirm that a significant diuresis is elicited by iv veratridine.

Materials and Methods. Experiments were performed on mongrel bitches ranging in weight from 12.3 to 22.8 kg. Studies were performed on 9 animals anesthetized with pentobarbital (30 mg/kg iv) and on 3 animals anesthetized with a combination of morphine (1 mg/kg sc) and chloralose (80 mg/kg iv). The chloralose was dissolved in polyethylene glycol (100 mg/ml). Catheters were inserted into an external jugular vein, a tributary of a femoral vein, and a branch of a femoral artery. The tips of the venous catheters were placed close to the right atrium. Two dogs were prepared for chronic use by implanting the vascular catheters several days prior to an experiment. Urine was collected at 10 min intervals through an indwelling bladder catheter. Blood samples for creatinine analysis were withdrawn at the midpoint of each urine collection period.

After urine flow was relatively constant for three 10 min periods, veratridine[2] at a dose comparable to that used by Thomas (1) (approx 6 μg/kg) was injected through the jugular catheter which was then flushed immediately with isotonic saline. The veratridine was dissolved in slightly acidified saline (100 μg/ml). Recording of hemodynamic and renal data was continued for 1 hr following the injection. Arterial blood samples for ADH determination were drawn 5 min before veratridine administration and 5, 20, and 60 min after injection of the drug. The first two samples were replaced with the simultaneous iv infusion of an equal volume of 6% dextran in normal saline and the subsequent two were replaced with red blood cells saved from the previous samples and resuspended in normal saline.

The clearance of creatinine was used as an estimate of glomerular filtration rate. Animals received a priming dose of 20 mg/kg and a continuously administered maintenance dose of 0.75 mg kg^{-1} min^{-1}. In the experiments performed on animals anesthetized with pentobarbital, the mainten-

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[2] Obtained from Aldrich Chemical Co., Inc., Milwaukee, WI 53210.

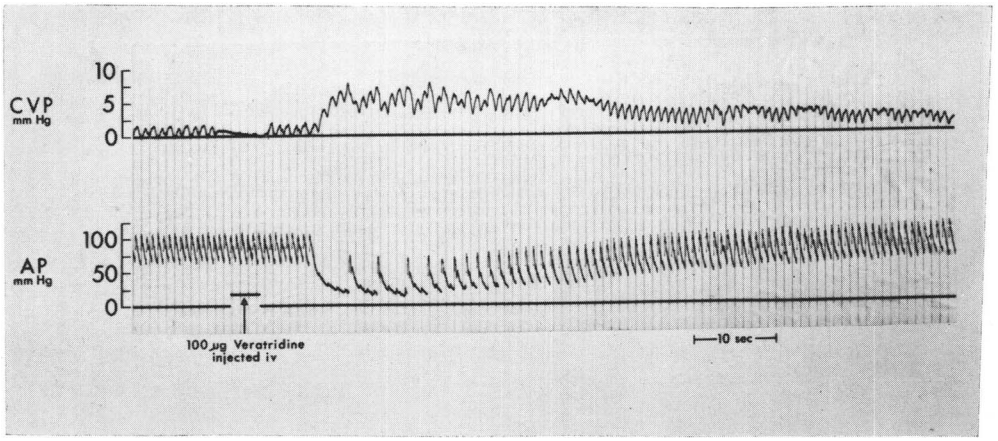

FIG. 1. Changes in hemodynamics elicited by injection of veratridine into a dog anesthetized with pentobarbital. CVP = central venous pressure; AP = aortic pressure.

ance dose was dissolved in normal saline and infused intravenously at a rate of 0.58 ml/min. In the experiments performed on animals anesthetized with morphine and chloralose, the maintenance dose of creatinine was dissolved in 5% dextrose and water and infused at a rate of 0.13 ml/min. Creatinine determinations were made with a Technicon AutoAnalyzer.

Arterial and central venous pressures were measured at the end of each urine collection period with Statham P23Db transducers and recorded on an Electronics for Medicine DR-8 recorder. Pulse rate was determined from the arterial pressure recording.

Aliquots of plasma (15–18 ml) for ADH determination were extracted and concentrated to a final 1.0 ml volume and then assayed in the hydrated, ethanol-anesthetized rat. Our previously described bioassay procedure (4) was modified by placing the assay rats in an incubator maintained at 34° and infusing them intravenously with a solution containing 0.3% NaCl, 1.6% glucose, and 2% ethanol at a rate of 0.26 ml/min (5). No sample has been included in the results unless at least two injections of USP posterior pituitary reference standard, at two dose levels, and two injections of sample were assayed on the same rat.

Sodium concentrations were determined in duplicate by flame photometry. The *t* test for paired samples was used for statistical evaluation.

Results. The typical hemodynamic response observed after injection of veratridine is shown in Fig. 1. Transient bradycardia, systemic hypotension, and an increase in central venous pressure consistently followed the injection.

Table I contains renal and hemodynamic data obtained before and after veratridine injection into dogs anesthetized with pentobarbital. Although urine flow and sodium excretion were not changed significantly by iv veratridine, there was a tendency for both of these variables to increase after the initial 10 min period following drug administration. The clearance of creatinine was significantly reduced in the collection period immediately after veratridine administration and was increased significantly 40 min after injection.

Central venous pressure and heart rate, except for the initial, transient changes (Fig. 1), were unaltered throughout the experimental period. Mean arterial pressure was significantly reduced 10 min after veratridine was given.

Ten experiments were performed on 3 dogs anesthetized with morphine and chloralose. In all cases, the response to veratridine qualitatively resembled that which occurred in the dogs anesthetized with pentobarbital. Renal and hemodynamic data from a representative experiment appear in Table II.

Satisfactory ADH determinations were made on all four blood samples in the 9 ex-

TABLE I. Effects of Veratridine on Renal Function and Hemodynamics.[a]

$n = 9$	Control			Postinjection					
minutes	−30 to −20	−20 to −10	−10 to 0	0 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60
V	0.42 ± 0.14	0.46 ± 0.15	0.44 ± 0.15	0.43 ± 0.17	0.60 ± 0.23	0.65 ± 0.26	0.79 ± 0.28	0.78 ± 0.29	0.73 ± 0.25
$U_{Na}V$	2.25 ± 0.71	2.10 ± 0.72	1.94 ± 0.73	2.22 ± 1.02	3.25 ± 1.52	3.14 ± 1.35	4.24 ± 1.74	4.23 ± 1.76	4.41 ± 1.78
C_{Cr}		75 ± 3	70 ± 4	67 ± 5[b]	94 ± 12	86 ± 10	88 ± 6[b]	90 ± 16	87 ± 8
MAP	106 ± 8	104 ± 7	105 ± 7	98 ± 7[b]	102 ± 7	107 ± 9	107 ± 8	106 ± 8	105 ± 8
CVP	2.6 ± 0.7	2.7 ± 0.7	2.8 ± 0.8	2.3 ± 0.9	2.2 ± 0.9	2.5 ± 1.0	2.1 ± 0.9	2.8 ± 1.0	2.2 ± 1.1
HR	114 ± 12	111 ± 10	111 ± 11	114 ± 15	113 ± 12	123 ± 11	121 ± 12	128 ± 12	130 ± 13

[a] Values are the mean ± SE. V = urine flow (ml/min); $U_{Na}V$ = sodium excretion (μEq/min/kg); C_{Cr} = clearance of creatinine (ml/min); MAP = mean arterial pressure (mm Hg); CVP = central venous pressure (mm Hg); HR = heart rate (beats/min).

[b] $p < .05$.

periments performed on dogs anesthetized with pentobarbital and in 9 of the 10 experiments performed on dogs anesthetized with morphine–chloralose. These data appear in Table III. Plasma ADH levels were significantly elevated 5 min after injection of veratridine in dogs anesthetized with pentobarbital and had returned to control levels by 20 min after injection. A secondary increase was noted 60 min after veratridine was given but it is difficult to attribute this increase directly to the effects of veratridine. ADH levels also were elevated 5 min after veratridine was given in 7 of the 9 experiments with morphine–chloralose anesthetic (Table III). Because these data were obtained from only three animals, statistical evaluation is not included for this group.

Discussion. This study demonstrates that plasma ADH concentration is significantly increased 5 min after veratridine is given intravenously. In evaluating these results, one must consider that the half-life of circulating ADH in dogs is from 4.9 to 7.5 min (6), and that the stimulation of cardiac receptors by veratridine reaches a maximum within 7–70 sec and usually has ended within 4 min after iv administration (2). A predominant inhibition of ADH secretion from any cardiac receptors therefore should have been evident in the plasma sample obtained 5 min after veratridine was given. The finding that ADH was significantly increased at that time is not compatible with the suggestion of Thomas (1) that the drug alters renal function primarily via atrial type B receptors, at least not if one accepts the hypothesis that ADH levels are influenced by left atrial type B receptors. Stimulation of these receptors is believed to cause an increase in urine flow which is mediated, at least in part, by a decrease in circulating ADH (3). We have pointed out elsewhere that some evidence does not support this hypothesis (4).

It is tempting to attribute the increase in plasma ADH at 5 min simply to the initial hypotensive effect of veratridine. This is hazardous, however, because veratridine and related veratrum alkaloids produce diverse pharmacological effects. They have been

shown to alter the activity of cutaneous receptors, pulmonary stretch receptors, carotid and aortic arch baroreceptors, right and left ventricular pressure receptors, type A and type B left atrial receptors, coronary mechanoreceptors, the endings of muscle spindles, and nerve fibers in general (7). These widespread effects of veratridine, coupled with the results of the present study, argue against the suggestion (1) that veratridine might offer a pharmacological approach to the investigation of atrial receptor involvement in fluid volume regulation.

Changes in urine flow following veratridine in our experiments were considerably less marked than those reported by Thomas (1). In the pentobarbital series (Table I) the small increase in urine flow was not significant statistically. It seemed possible however, that this minimal urine flow response could have been due to a depressant effect of pentobarbital anesthesia. Chloralose, an anesthetic which has little, if any, depressant effect on cardiovascular reflexes (8, 9) was used in Thomas's studies. Consequently, we performed the additional experiments with morphine–chloralose anesthetic in amounts identical to those used by Thomas (1) to test the possibility that veratridine might produce a markedly different renal (and ADH) response in animals anesthetized with these drugs. Clearly the data obtained argue strongly against this possibility. We are unable to explain why the renal response in our experiments differ from the results which Thomas obtained.

Summary. These experiments were designed to test the hypothesis that veratridine given intravenously causes a diuresis which is mediated by a decrease in plasma ADH. The results demonstrate that plasma ADH is not reduced, but rather is temporarily increased following veratridine administration. It is difficult to say which of the diverse pharmacological effects of veratridine produces the increase in ADH.

Urine flow decreases immediately after veratridine is given and then tends to increase, but the increase was not significant statistically in the present experiments.

TABLE II. Effects of Veratridine on Renal Function and Hemodynamics in a Dog Under Morphine-Chloralose Anesthesia.[a]

	Control			Postinjection					
(min)	−30 to −20	−20 to −10	−10 to 0	0 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60
V	0.84	0.83	0.80	0.77	0.77	0.83	0.86	0.88	0.85
$U_{Na}V$	1.71	1.44	1.19	0.96	0.84	0.83	1.18	1.21	1.03
C_{Cr}		48	50	49	48	62	55	59	60
MAP	98	98	98	100	100	100	100	105	113
CVP	5.0	5.5	5.3	4.3	6.0	6.0	5.8	5.5	6.5
HR	69	70	82	96	112	123	96	104	81

[a] See Table I for explanation of abbreviations.

TABLE III. Effect of Veratridine on Plasma ADH.[a]

	Dog no.	Control	After injection (min) 5	20	60
Pentobarbital experiments					
	1	1.9	6.2	2.4	3.1
	2	1.3	9.4	4.2	4.6
	3	3.4	0.9	1.0	2.9
	4	1.8	4.8	1.7	1.6
	5	1.3	2.5	2.5	3.7
	6	7.9	16.7	5.2	7.8
	7	1.0	2.0	1.0	1.1
	8	1.1	2.2	1.3	4.4
	9	4.5	13.5	5.2	5.7
	$\bar{X} \pm$ SE	2.7 ± 0.8	6.5 ± 1.9	2.7 ± 0.6	3.9 ± 0.7
			$p < .025$	$p > .95$	$p < .05$
Morphine–chloralose experiments					
	10[b]	2.8 ± 0.9	13.3 ± 3.8	2.0 ± 0.3	2.1 ± 0.4
	11[c]	7.3	24.5	4.8	4.9
	12[d]	0.7	4.9	2.6	2.1

[a] Values (μU/ml).
[b] Values are the mean of 6 experiments performed over a 10 day period.
[c] Values are the mean of 2 experiments performed on separate days.
[d] Values are for the single experiment performed on this animal.

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