Effect of Hydroxyzine* on Urine Flow in the Dog.† (25578)

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Antidiuresis implicating liberation of the antidiuretic hormone has been well established following administration of several agents which depress the central nervous system(1). More recently, reserpine(2) and chlorpromazine(3), both tranquillizing agents which also exert an effect on the nervous system, have been reported to inhibit water diuresis. While conducting preliminary experiments on another tranquillizing agent, hydroxyzine, a decrease in urine flow was noted in dogs. As a result this communication presents findings concerning the effect of hydroxyzine on urine flow and its mechanism of action. Sanchez and Davis(4) recently reported antidiuresis in hydrated rats which had received hydroxyzine by intraperitoneal injection.

Methods. All experiments were performed on trained unanesthetized dogs. Normal and diabetes insipidus dogs were used. Neurohypophysectomies were performed by the temporal approach in which a high stalk section was made.‡ The diabetes insipidus animals were not used until a month following operation, and daily urine output was in excess of 2000 ml. Two types of experimental procedures were employed. In the first series, experiments were conducted similar in principle to that described by de Bodo(5). Animals were kept in metabolism cages and hydrated with 50 ml/kg of water. At the end of 3 hours the bladder was emptied by catheterization and the same amount of water was again given. Excretion of the second water load was used for evaluating the effect of hydroxyzine. The drug was injected 40 minutes after the second water load was administered and urine excreted during the 40 minutes interval subtracted from the total water load since the drug had no effect on this fraction. Hydroxyzine was administered intravenously in a dose of 5 mg/kg over a 5 to 10 minute interval. In the second series of experiments the animals were hydrated with 30 ml/kg of water 1 hour prior to experiment. Throughout the experiment glucose 5% in water was infused at a constant rate of 3 ml/minute. Following a control period, hydroxyzine was infused intravenously in a dose of 5 mg/kg over a 30 minute period. Urine was collected for an additional 2½ hours following cessation of hydroxyzine infusion. Determinations of glomerular filtration rate, renal plasma flow, osmolar and "free" water clearance were obtained by methods previously described(6). Statistical analysis of the data was performed by the method of Mather(7) in which values obtained during the hydroxyzine infusion and each subsequent hour were compared to control values.

Results. Table I shows the effect of hydroxyzine on urine flow during water diuresis in normal dogs. Values given are average per cent of volumes obtained in each experiment; figures in parenthesis represent minimum and maximum amount of the water load excreted.

TABLE I. Effect of Hydroxyzine (5 mg/kg) on Water Diuresis in Normal Dogs.

Dog No.	No. of exp.	Type of exp.	% of second water load excreted at 3 hr
1	3	Control	98 (93, 102)
	3	Drug	67 (61, 74)
2	4	Control	96 (94, 100)
	4	Drug	75 (65, 83)
3	2	Drug	74 (76, 73)
4	3	Control	99 (96, 103)
	3	Drug	71 (59, 80)
5	2	Drug	69 (72, 66)
6	2	"	66 (61, 71)
7	1	"	67
8	1	"	74
9	3	Control	93 (94, 105)
	3	Drug	77 (74, 80)
10	2	Drug	86 (82, 90)
11	3	Control	95 (91, 98)
	3	Drug	73 (62, 80)

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TABLE II. Effect of Hydroxyzine (5 mg/kg) on Glomerular Filtration Rate, Urine Flow, Osmolar and Free Water Balance.

GFR, ml/min.				V, ml/min.				C_{osm}, ml/min.				C_{H_2O}, ml/min.			
C	I	PI 1 hr	PI 2 hr	C	I	PI 1 hr	PI 2 hr	C	I	PI 1 hr	PI 2 hr	C	I	PI 1 hr	PI 2 hr
60	59	56	57	4.5	4.0	1.6	1.5	.7	.7	1.1	.8	3.8	3.3	.5	.7
71	71	59	65	5.6	6.0	2.8	3.0	1.4	1.2	1.1	1.2	4.2	4.8	1.7	1.8
69	79	79	73	4.9	6.0	2.8	2.8	.7	.7	.9	1.0	4.2	5.3	1.9	1.7
91	98	95	84	6.3	5.4	4.7	1.9	1.1	1.0	1.2	1.4	5.2	4.4	3.5	.5
67	71	72	74	4.2	4.2	3.5	3.5	.7	.6	.6	.6	3.5	3.6	2.9	2.9
84	83	84	78	5.4	5.5	4.4	3.1	.9	.7	.8	.7	4.5	4.8	3.6	2.4
59	59	68	64	5.0	6.7	4.1	1.7	.4	.5	.9	.6	4.5	6.2	3.2	1.1
55	58	53	56	5.0	4.8	2.5	2.3	.9	.9	.7	.8	4.1	3.9	1.8	1.5
64	59	63	66	4.7	4.6	2.9	2.8	1.1	1.2	1.0	1.0	3.6	3.4	1.9	1.7
68.9*	70.8	69.9	68.5	5.1	5.2	3.2	2.5	.9	.8	.9	.9	4.2	4.4	2.3	1.6
±3.9†	±4.6	±4.6	±3.1	±.2	±.3	±.3	±.2	±.09	±.08	±.06	±.09	±.2	±.3	±.3	±.2

* Mean. † S.E.

Volume of urine excreted in 3 hours by the control animals was an average of 96.2%. In the experiments where hydroxyzine was administered, a definite decrease in urine output occurred, the average being 72.6% of the second water load during the 3 hour period. These results indicate that hydroxyzine decreased urine output in dogs undergoing water diuresis, thus raising the possibility that this effect may have occurred either because of hemodynamic changes or a specific effect of hydroxyzine on water reabsorption. Results of the experiments where hydroxyzine was infused for 30 minutes are illustrated in Table II. The drug also produced a decrease in urine flow. This occurred only during the period following cessation of hydroxyzine. No change in glomerular filtration rate occurred in these experiments $P>0.05$). Similarly, hydroxyzine caused no change in renal plasma flow. These findings indicate that the decrease in urine flow was not the result of any hemodynamic changes, suggesting a specific antidiuretic effect. Determination of osmolar clearance revealed no significant change throughout the experiment ($P > 0.05$); however, a significant fall ($P < 0.05$) in "free" water clearance occurred during the period following cessation of hydroxyzine. These results indicate that hydroxyzine influenced only "free" water reabsorption. It is of interest to note that the antidiuretic effect did not occur immediately as is generally observed with other antidiuretic agents. This delayed onset could imply that antidiuresis did not occur until sufficient time had elapsed for hydroxyzine to cross the blood brain barrier. However, the fact that some degree of tranquillization occurs clinically in most individuals within 15 to 30 minutes, when given orally, indicates the drug does cross the blood brain barrier rapidly, and would not explain the delay in onset. Another possibility is that the response is not due to hydroxyzine *per se,* but rather to a metabolic product of hydroxyzine. Unfortunately, no chemical test is available for determination of hydroxyzine in tissues so this delayed onset can not be explained.

The effect of hydroxyzine on urine flow in diabetes insipidus dogs is summarized in Table III. Following infusion of hydroxyzine there was no change in urine flow in contrast to the decrease noted in normal animals. These re-

TABLE III. Effect of Hydroxyzine (5 mg/kg) on Urine Flow in Diabetes Insipidus Dogs.

Dog	Exp. No.	Control	Hydroxyzine	Post-infusion 1 hr	Post-infusion 2 hr
		ml/min.			
1	1	4.4	3.9	4.0	5.4
	2	5.0	4.6	6.1	5.3
	3	4.3	3.8	4.7	4.9
	4	3.7	3.3	4.8	4.7
2	1	4.7	5.6	4.6	5.2
	2	3.0	4.8	4.3	6.1
	3	4.3	4.8	5.4	4.8
	4	5.0	4.1	4.7	5.4
3	1	3.8	4.2	4.8	4.1
	2	5.4	4.9	5.2	5.9
	3	4.3	4.6	4.0	4.5
	4	3.6	3.9	4.0	3.4
Mean		4.3	4.4	4.8	5.0
S.E.		±.2	±.2	±.2	±.3

sults indicate that hydroxyzine stimulated release of the antidiuretic hormone in normal dogs, otherwise similar results would have been obtained in both types of animals. In addition, measurement of osmolar and "free" water clearance in 4 experiments in diabetes insipidus dogs showed no change from the control values.

Summary. Intravenous administration of hydroxyzine to unanesthetized dogs in doses of 5 mg/kg produced a decrease in urine flow following cessation of the drug in absence of any hemodynamic changes. In contrast to response in normal dogs there was no change in urine flow in diabetes insipidus animals. These results indicate hydroxyzine stimulated release of the antidiuretic hormone under conditions described here.

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Response to Stress: Differing Responses of Atherosclerotic and Normal Dog to Electric Shock or Cold.*† (25579)

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Inability to adapt successfully to stressful situations may be a factor in development of cardiovascular pathology. Although the role of the autonomic nervous system and hypothalamic-pituitary-adrenal axis in response to stress has received intensive study, the interrelations between this system and cardiovascular pathology are virtually unexplored. This report describes differing response of atherosclerotic and normal (non-atherosclerotic) dogs to stresses of electric shock and cold.

Methods. Thirty-five dogs were used. Twenty-one (9 beagles and 12 mongrels) were made atherosclerotic by maintenance on standard thiouracil and cholesterol diet (consisting of 50 mg thiouracil/kg body weight and kibble containing cholesterol prepared with ether solvent to provide daily cholesterol intake of 750 mg/kilo body weight) as previously reported by this group(1). These dogs were maintained on the atherogenic regimen for 6 months to 2 years. The remaining 14 dogs (9 beagles and 5 mongrels) served as controls and received standard kibble diet. *Electric shock.* The 21 atherosclerotic dogs and 14 normal dogs were subjected to electric shock. Each dog was anesthetized with sodium pentobarbital, after which 5 shocks were administered across frontal lobes within 15 minutes by electric shock machine delivering 450 milliamperes of 0.7 sec. duration. Urine samples were collected hourly by catheter for 3 hours prior to and 3 hours following shock treatment. Urine was analyzed for corticoids by the Heard-Sobel method(2) and for creatinine by the method of Bonsnes and Tausky(3). *Cold stress.* Four normal dogs and 4 atherosclerotic dogs were placed in metabolic cages. A minimum of three 24-hour urine collections at room temperature served as controls for each dog. Cold stress consisted of

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