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Arnold M. Moses, Joan Howanitz, Marcia Van Gemert, Myron Miller

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Research Article

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ARNOLD M. MOSES, JOAN HOWANITZ, MARCIA VAN GEMERT, and MYRON MILLER

From the Veterans Administration Hospital and Departments of Medicine and Pharmacology, State University of New York, Upstate Medical Center, Syracuse, New York 13210

ABSTRACT Normal subjects and patients with antidiuretic hormone (ADH) deficiency were studied to determine the mechanism of the antidiuretic action of clofibrate. Before clofibrate treatment, the patients' ability to concentrate urine with a standardized dehydration procedure correlated with the amount of ADH which was excreted. During clofibrate administration all six patients with ADH deficiency developed an antidiuresis which was like that of ADH, since there was no change in sodium, potassium, total solute, or creatinine excretion. There was a correlation between the patients' ability to concentrate urine during dehydration and the subsequent response to clofibrate, and the excretion of ADH during dehydration correlated with the excretion of ADH on clofibrate therapy. Clofibrate-induced antidiuresis in these patients was partially overcome by ethanol and by water loading. Clofibrate interfered with the ability of patients and subjects to excrete a water load and prevented the water load from inhibiting ADH excretion in the normal subjects. These studies suggested that clofibrate was acting through endogenous ADH and this thesis was supported by the failure of clofibrate to produce an antidiuresis when injected into rats with total ADH deficiency (Brattleboro strain) although an antidiuresis was produced in water-loaded normal rats. When the drug was injected into Brattleboro rats with exogenous ADH, clofibrate either did not alter or it inhibited the action of the ADH. The data demonstrate that clofibrate has a significant ADH-like action. This action appears to be mediated through the release of endogenous ADH.

INTRODUCTION

There are obvious advantages in using oral agents in the treatment of diabetes insipidus. Chlorpropamide is effective in treating most patients with hypothalamic diabetes insipidus (1) but may produce symptomatic hypoglycemia (2). An oral agent capable of producing an antidiuresis without side effects would represent a further advancement in the treatment of diabetes insipidus. Clofibrate, a commonly used hypolipidemic agent with relatively few side effects, has recently been reported to have a water-retaining action in patients with diabetes insipidus (3–5). There is no information on the mechanism of this antidiuresis. We therefore investigated the extent and mechanism of the reported antidiuretic action of clofibrate.

METHODS

Six patients with diabetes insipidus were investigated. The diagnosis of the diabetes insipidus was based on a dehydration test previously described (6). In this procedure, dehydration is carried out until there is a plateau in urine osmolality and the osmolality thus attained is compared to the urine osmolality which follows the subsequent injection of antidiuretic hormone (ADH).[1] In patients with ADH deficiency the urine osmolality reached at the end of the period of dehydration increases further by at least 9% after the injection of ADH, while in normal subjects no further increase in urine osmolality occurs after the injection of exogenous ADH. In the six patients the plasma osmolalities and maximum urine osmolalities at the plateau before the injection of ADH, as well as the corresponding free water clearances and urinary ADH excretions, are indicated in Table I along with other clinical features.

The patients were studied on the metabolic ward of the Adult Clinical Center of the State University Hospital, Syracuse, N. Y., while being maintained on a daily intake of 100 meq of sodium, 80 meq of potassium, and water ad lib. unless otherwise indicated. All antidiuretic therapy was stopped before initiation of the studies. Urine was collected hourly from 8:00 a.m. until noon and then in a single collection over the next 20 h. Each specimen was measured for volume, osmolality, and creatinine, sodium, potassium, and ADH excretion. The patients were given an oral water load of 20 ml/kg body weight, with voided urine volume replaced by an equal volume of tap water every 15 min for 4 h. The patients were then treated with clofibrate, 500 mg orally every 6 h. After 3–5 days of treatment (one exception indicated by * in Table III) the studies were repeated and the 24 h excretion data, with and without clofibrate, were com-

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[1] *Abbreviations used in this paper:* ADH, antidiuretic hormone; PTO, Pitressin tannate in oil.

TABLE I

Clinical Data on Patients with Diabetes Insipidus in Order of Increasing Ability to Concentrate Urine on Dehydration

Patient	Sex	Age	Etiology	Plasma osmolality	Maximum Uosm	Minimum CH_2O	Maximum urinary ADH excretion
				mosmol/kg	*mosmol/kg*	*ml/h*	*μU/h*
R. H.	M	27	Idiopathic	324	102	347.5	450
F. C.	M	45	Idiopathic	304	183	65.2	0
S. C.	M	37	Idiopathic	308	292	1.0	640
A. V.	F	42	Posthypophysectomy	306	306	0	800
G. C.	M	28	Posttraumatic	297	513	−32.7	1660
M. M.	F	59	Idiopathic	297	592	−39.7	1020

pared. In addition, the mean values for volume, free water clearance, and osmolality during the last three periods of the water load were compared before and during clofibrate treatment. During clofibrate therapy and while on ad lib. fluid intake the patients were given 25 ml of 95% ethanol in juice at 8:00 a.m. and 20 ml at 9, 10, and 11:00 a.m. Hourly urine volumes, osmolalities, and free water clearances were compared with results obtained during the same hours when they were treated with clofibrate and fluids ad lib. but no ethanol.

13 normal male subjects, in their early to mid 20's, were subjected to a maintained water load of 20 ml/kg body weight until urine volume and osmolality reached a constant level for three consecutive 15-min collection periods. Each urine specimen was measured for volume, osmolality, and creatinine and ADH excretion. Identical studies were repeated, in random order, after 11 subjects had taken 500 mg of clofibrate four times a day for 2 days and 1500 mg 1 h before the initiation of the water load. Five subjects, including three studied under the first dosage regimen, had repeat water loads after treatment with clofibrate in the dosage of 1 g at 3, 2, and 1 h before the beginning of the water load. There were no detectable differences in the responses to the two dosage regimens.

10 normal Long Evans rats were repeatedly given a water load of 5 ml/100 g body weight through a stomach tube after overnight fasting. After the rats were adjusted to the procedure, urine was collected hourly for 3 h after the water-loading procedure and measured for volume and osmolality. Half of the rats were injected intramuscularly daily with 40 mg of clofibrate 1 h before the water load and half received peanut oil injections. 2 wk later the experiments were repeated in reverse order of clofibrate and peanut oil. Minimal urine osmolality, maximum hourly flow rates, and maximum free water clearances for 2 days were averaged and the data obtained with and without clofibrate administration were compared.

Additional studies were conducted in rats with hereditary hypothalamic diabetes insipidus (Brattleboro strain) which are totally devoid of ADH (7). Rats were acclimated in individual metabolic cages for at least 2 days before the studies and were fed Sturdy rat food (Sturdy Dog Food Co., Syracuse, N. Y.) and water ad lib. 40 mg of clofibrate in peanut oil was injected subcutaneously and 2 h later either saline or 5, 7.5, 10, or 20 mU of aqueous ADH (Pitressin, Parke, Davis and Co., Detroit, Mich.) was injected subcutaneously. Urine was collected over the next 4 h and measured for volume and osmolality. Experiments were repeated without clofibrate injection (random order) and the responses to ADH, with and without clofibrate, were compared. In another experiment, 40 mg of clofibrate was injected daily for 3 days into the diabetes insipidus rats and on the 1st day 3, 10, or 30 mU/100 g body weight of Pitressin tannate in oil (PTO) was injected intramuscularly and urine was collected daily for the next 3 days and measured for volume and osmolality. Experiments were repeated without clofibrate (random order) and the responses to PTO, with and without clofibrate, were compared.

Urine and plasma osmolalities were determined by freezing point depression with an Advanced Instruments Cryomatic osmometer (Advanced Instruments, Inc., Needham Heights, Mass.). Sodium and potassium were determined by an Instrumentation Laboratory flame photometer (Instrumentation Laboratory, Inc., Lexington, Mass.). Creatinine was determined by the Auto-Analyzer (Technicon Instruments Corporation, Ardsley, N. Y.).

Urinary ADH was quantitated by radioimmunoassay using a previously described method (8, 9). To test the possibility that clofibrate might react in the assay and give a false positive value for ADH, clofibrate was dissolved in the assay buffer (0.01 M PO_4—0.15 M NaCl—1% bovine serum albumin, pH 7.4) in concentrations ranging from 0.125 to 1 mg/ml and the solution was assayed for ADH activity. Studies were also done to exclude the possibility that urinary metabolites of clofibrate could react in the assay system. A 24 h urine specimen was collected from a normal subject who had received clofibrate, 2 g daily, for 2 days. 25-ml samples of the urine specimen were extracted and concentrated (8, 9) and 1 ml portions of the extracts were incubated with either 1 ml of buffer or of tyrosinase (0.1 mg/ml in 0.1 M PO_4 buffer pH 7.5) at 37°C for 90 min. After incubation, the mixtures were boiled for 10 min to inactivate the tyrosinase and then assayed for residual ADH activity. Incubation of arginine vasopressin with tyrosinase under these conditions has previously been shown to result in loss of approximately 90% of immunoreactivity.

The significance of procedures was determined by *t* test for paired comparisons.

RESULTS

The administration of clofibrate to patients with diabetes insipidus on ad lib. fluid intake resulted in a significant antidiuresis with mean urine volume decreasing from 280 ml/h to 141, mean free water clearance

TABLE II

Response to Clofibrate (Clo) Treatment in Patients with ADH Deficiency while on Ad Lib. Fluid Intake

Patient	Urine volume		Free water clearance		Osmolal clearance		Urine osmolality		Creatinine excretion		Sodium excretion		Potassium excretion		ADH excretion	
	No treatment	Clo	No treatment	Clo	No treatment	Clo	No treatment	Clo	No treatment	Clo	No treatment	Clo	No treatment	Clo	No treatment	Clo
	ml/h		*ml/h*		*ml/h*		*mosmol/kg*		*mg/h*		*meq/h*		*meq/h*		*μU/h*	
R. H.	512	299	350	143	162	156	92	158	49.9	56.7	5.55	5.52	4.12	3.26	104	93
F. C.	366	96	230	−59	136	155	113	450	58.0	59.7	4.20	7.10	1.20	4.32	0	125
S. C.	323	152	201	28	122	124	112	247	37.1	40.3	8.01	12.10	5.14	4.41	0	64
A. V.	156	94	75	−1	81	94	154	298	44.6	41.2	2.02	2.89	2.80	2.31	85	184
G. C.	131	114	13	−38	118	152	264	400	73.9	65.4	0.95	3.96	0.26	0.29	811	469
M. M.	193	91	82	−10	114	101	177	348	46.0	42.7	4.75	3.12	2.83	2.59	79	241
Mean	280	141*	158	10*	122	130	152	317*	51.6	51.0	4.25	5.78	2.73	2.85	180	196
SEM	60	33	51	29	11	11	26	43	5.3	4.5	1.03	1.42	0.74	0.62	128	60

* $P < 0.02$.

decreasing from 158 to 10 ml/h, and mean urine osmolality increasing from 152 to 317 mosmol/kg. The antidiuresis was associated with an increase in urinary ADH excretion in four of the six patients. There was no change in osmolal clearance or creatinine, sodium or potassium excretion (Table II and Fig. 1). When the patients with diabetes insipidus on clofibrate treatment were given either ethanol or a maintained water load a significant diuresis resulted over the 4 h of the procedures for all three parameters measured (Table III). When the patients with diabetes insipidus were subjected to maintained water loads, they excreted a more concentrated urine and had a lesser urine volume and free water clearance during treatment with clofibrate (Fig. 1). Before clofibrate therapy the maximum urine volume was 12.4±1.0 ml/min in contrast to 6.2±1.0 ($P < 0.02$) on clofibrate; maximum free water clearance was 10.0±0.8 ml/min in contrast to 3.9±0.7 ($P < 0.01$) on clofibrate; and minimum urine osmolality was 56.3±4.6 mosmol/kg in contrast to 115.5±8.9 ($P < 0.01$) on clofibrate. The osmolal clearance was 2.4 ml/min with and without clofibrate. In the six ADH-deficient patients there was a significant correlation between the maximum urinary ADH excreted during the dehydration test and the urinary ADH excretion when the same subjects were subsequently treated with clofibrate and given fluids ad lib. (Fig. 2).

The normal subjects who were given a maintained water load with and without clofibrate therapy had a lesser ability to excrete the water load while on drug therapy. The maximum urinary volume was 16.0±0.7 ml/min without treatment and 13.8±1.1 ml/min on clofibrate ($P < 0.02$); maximum free water clearance was 12.1±0.5 ml/min in contrast to 9.7±0.9 ml/min on clofibrate ($P < 0.005$); and minimum urinary osmolality was 68.0±2.6 mosmol/kg without drug therapy and 87.0±4.7 on clofibrate treatment ($P < 0.005$). During these experiments, urinary ADH excretion without drug therapy was 6.4±2.5 μU/min as compared to 30.3±9.8 μU/min when the subjects were treated with clofibrate ($P < 0.05$). Further, when urinary ADH excretion in the 16 clofibrate-treated water-loaded normal subjects was compared with urinary ADH excretion in a larger group of 28 untreated water-loaded normal subjects, who had urinary ADH excretion of 4.7±1.4 μU/min, the clofibrate

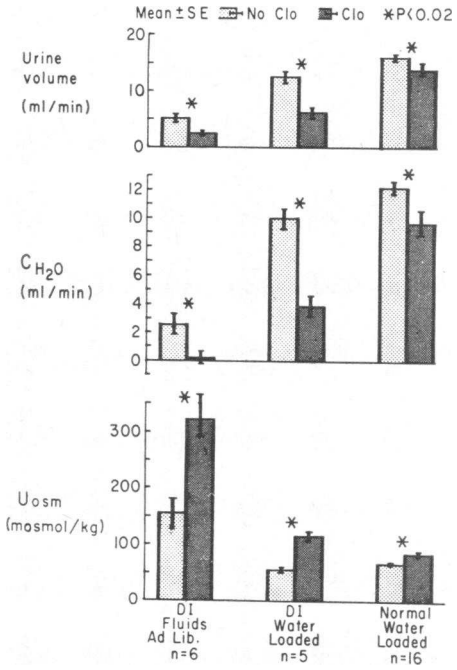

FIGURE 1 **Effect of clofibrate (Clo) on urine volume, free water clearance, and osmolality in diabetes insipidus patients on ad lib. fluid intake, and in diabetes insipidus patients and normal subjects who were given a maintained 20 ml/kg body weight water load. A clofibrate-induced antidiuresis was reflected in all three measurements in all three clinical circumstances.**

TABLE III

Response of ADH-Deficient Patients to Clofibrate (Clo) Treatment and to Ethanol and Water Load while Receiving Clofibrate

Patient	Hour	Urine volumes			Free water clearance			Urine osmolality		
		Clo	Clo +ethanol	Clo +water load	Clo	Clo +ethanol	Clo +water load	Clo	Clo +ethanol	Clo +water load
		ml/h			*ml/h*			*mosmol/kg*		
R. H.	1	392	554	623	234	368	364	122	102	122
	2	542	750	473	342	500	322	112	101	93
	3	548	408	534	350	223	376	110	137	87
	4	428	408	456	250	223	322	126	137	86
F. C.	1	170*	185	218	107*	48	84	109*	194	179
	2	455*	365	323	264*	201	213	123*	118	99
	3	225*	323	278	106*	182	168	155*	115	115
	4	170*	310	215	40*	164	106	225*	124	147
S. C.	1	56	198	104	−26	88	17	428	165	250
	2	140	430	320	15	261	172	259	117	138
	3	204	470	436	40	278	241	234	122	133
	4	235	435	395	47	244	219	233	131	133
A. V.	1	47	57	232	−25	−12	−68	454	360	379
	2	68	260	322	−24	26	185	399	266	134
	3	100	200	531	26	68	343	218	196	104
	4	90	239	—	20	119	—	231	149	—
M. M.	1	138	51	295	6	−15	90	280	378	203
	2	305	267	340	176	130	174	123	149	143
	3	140	410	280	8	248	150	276	115	135
	4	58	305	255	−35	178	153	467	121	117
Mean ±SEM	1	161±62	209±92	294±88	59±50	95±71	97±72	279±73	240±55	227±43
	2	302±90	414±90	356±30	155±70	224±79	213±28	203±56	150±30	121±10
	3	243±79	362±47	412±57	106±63	200±36	256±45	199±30	137±15	115±9
	4	196±65	339±36	330±57	64±49	186±22	200±47	256±56	132±5	121±13

* First day clofibrate.

Ethanol and water load both overcame the antidiuretic action of clofibrate ($P. < .01$).

effect was statistically greater ($P < 0.005$). There was no difference in osmolal clearance or creatinine excretion with or without drug therapy (Figs. 1 and 3).

Clofibrate solutions which ranged in concentration from 0.125 mg to 1 mg/ml failed to reveal any evidence of immunoreactivity in the assay system for ADH. An extract of urine from a normal subject who received clofibrate was incubated with tyrosinase and lost 85% of ADH immunoreactivity. These studies indicate that the ADH activity measured in the urine of subjects who received clofibrate is due to ADH and is not due to the presence of clofibrate or its metabolites.

The administration of clofibrate to the normal water-loaded rat significantly impaired excretion of the water load as measured by both volume and free water clearances (Table IV).

The administration of clofibrate to the rats with diabetes insipidus did not alter urinary flow or concentration, and in addition clofibrate did not affect the response to the injection of aqueous ADH (Table V). However, the administration of clofibrate daily along with the injection of PTO resulted in a significant enhancement of urinary volume on the 1st day after the injection of 3 mU/100 g body weight PTO and on the 3rd day after the administration of 30 mU of PTO/100 g body weight. In addition, when the data for the 3 day period after the injection of 30 mU/100 g body weight of PTO were pooled, clofibrate enhanced the excretion of water in terms of urinary volume ($P < 0.025$) and free water clearance ($P < 0.01$). There were no significant changes in osmolal clearance or urine osmolality in these experiments (Fig. 4). There was also no change in creatinine excretion.

DISCUSSION

Normal subjects, after overnight dehydration, excrete between 1200–4500 μU ADH/h (9). Only one ADH-deficient subject (G. C.) had urinary ADH excretion in

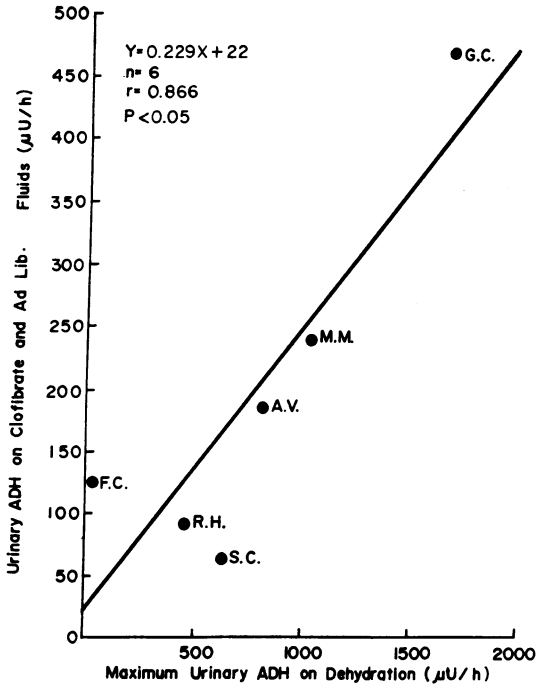

FIGURE 2 Relationship between the maximum urinary ADH which was excreted by six ADH-deficient patients during a standardized dehydration procedure, and the amount of urinary ADH which was excreted by these patients when they were treated with clofibrate and allowed to drink ad lib. The correlation was significant ($P < 0.05$).

this range after dehydration sufficient to result in a plateau in urine osmolality, and this was associated with a higher plasma osmolality than was found in normal subjects (9). The other five patients had urinary ADH after dehydration which ranged from undetectable to 1020 μU/h despite elevated plasma osmolalities (Table I). The data from the six ADH-deficient patients indicated a correlation between the ability to concentrate urine and the ability to excrete ADH during a dehydration procedure (Table I). This correlation has been commented upon previously (10) and appears to validate further the dehydration test as a means of assessing residual neurohypophyseal function (6). All of the patients studied, except F. C., had ADH which was releasable by dehydration. When the six ADH-deficient patients were treated with clofibrate and allowed fluids ad lib., they each developed a more concentrated urine with a decreased urine volume and free water clearance (Table II). This was associated with a decrease in plasma osmolality from 297.2±1.5 mosmol/kg to 291.6± 2.4. This is indicative of water retention. The antidiuresis was like that of ADH because it was not accompanied by a change in creatinine or electrolyte excretion or osmolal clearance. All of the patients had detectable ADH in the urine during clofibrate-induced antidiuresis and

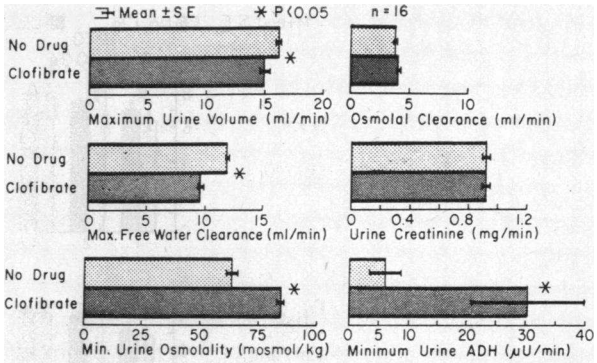

FIGURE 3 Influence of clofibrate on the ability of 16 normal subjects to excrete a maintained 20 ml/kg body weight water load. On clofibrate therapy, maximum urine volume and free water clearance were decreased, minimum urine osmolality and ADH were increased, and there was no change in osmolal clearance or creatinine excretion.

four of the six patients had more urinary ADH during clofibrate treatment than in the pretreatment urine specimens. The ability of the patients to excrete and presumably release ADH on dehydration correlated significantly with subsequent ADH excretion on clofibrate therapy (Fig. 2). This may indicate that residual releasable ADH is necessary for clofibrate to induce an antidiuresis. This is supported by the observation that clofibrate was unable to produce an antidiuresis in the rat which is completely devoid of ADH (Table IV).

Clinical indices of ADH activity also support the above conclusion. The minimum free water clearance obtained with dehydration (Table I) correlates with the free water clearance resulting from clofibrate therapy while on random fluid intake (Table II), ($P < 0.05$). In this group of patients, when the free water clearance on dehydration decreased to 65.2 ml/h or less, free water clearance on subsequent clofibrate therapy was 28 ml/h or less, which is a degree of polyuria which can often be quite well tolerated by the patient. The role of ADH in the clofibrate-induced antidiuresis is further supported by the data showing that a diuresis is induced by ethanol

TABLE IV

Influence of Clofibrate on Excretion of a Single Water Load in 10 Normal Rats

	Minimum Uosm	Maximum urine volume	Maximum C_{H_2O}
	mosmo/kg	*ml/h*	*ml/h*
No treatment	108.4±7.0	4.54±0.26	2.88±0.19
Clofibrate	141.2±18.6	3.73±0.26*	2.00±0.30*

Clofibrate administration caused an impaired excretion of the water load. Figures represent mean ±SEM.
* $P < 0.025$.

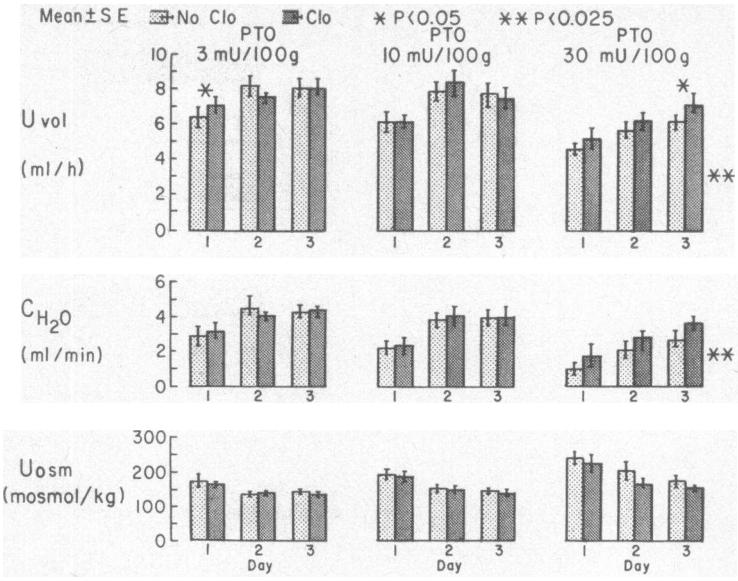

FIGURE 4 Effect of clofibrate (Clo) on urinary response over a 3 day period to the injection of PTO in eight diabetes insipidus rats. Clofibrate increased urine volume on the 1st day after the injection of 3 mU PTO/100 g body weight and on the 3rd day after the injection of 30 mu PTO/100 g ($P < 0.05$). Over the entire 3 day period after the injection of 30 mU PTO/100 g, clofibrate increased urine volume ($P < 0.025$) and free water clearance ($P < 0.01$).

and by water loading (Table III), both of which inhibit ADH release (11).

The antidiuretic response to clofibrate was also observed in normal subjects. A small but consistent ADH-like antidiuresis was exerted by clofibrate during a maintained water load and was associated with failure to suppress urinary ADH (Fig. 3). Like man, the ability of the normal rat to excrete a water load was interfered with by clofibrate (Table IV).

Since it is very unusual to find patients with complete ADH deficiency it was necessary to utilize the rat with hereditary hypothalamic diabetes insipidus (Brattleboro strain) to determine if clofibrate had an intrinsic antidiuretic action. No antidiuresis was found when the rats were given the largest amount of clofibrate they could tolerate without developing diarrhea (Table V).

Because of the reported action of chlorpropamide in augmenting the peripheral effect of ADH (12, 13), studies were carried out to determine if clofibrate had a similar mechanism of action. We were unable to demonstrate that clofibrate could increase the antidiuretic response to ADH by using the same protocol and amounts of aqueous ADH (12) and PTO (13) that had previously been shown to augment the peripheral action of ADH by chlorpropamide. There was in fact a diuretic action of clofibrate at 3 mU ADH/100 g of rat on day 1

TABLE V

Effect of Clofibrate (Clo) on Urinary Response over a 4 h Period to the Injection of Aqueous ADH in 12 Diabetes Insipidus Rats

Amount aqueous ADH	Urine volume		Free water clearance		Osmolal clearance		Urine osmolality	
	No Clo	Clo	No Clo	Clo	No Clo	Clo	No Clo	Clo
(mU)	ml/h		ml/h		ml/h		mosmol/kg	
0	7.35±0.81	8.16±0.54	4.08±0.55	4.59±0.41	3.27±0.31	3.57±0.23	136.6±5.9	132.6±7.1
5	5.54±0.64	5.35±0.62	2.12±0.40	1.97±0.42	3.41±0.31	3.37±0.30	200.4±13.6	198.1±11.7
7.5	5.28±0.38	4.68±0.51	1.88±0.24	1.61±0.29	3.40±0.21	3.07±0.28	196.5±7.0	211.0±17.1
10	3.94±0.34	4.30±0.31	1.09±0.22	1.30±0.20	2.84±0.15	3.01±0.17	228.1±15.0	214.2±9.5
20	4.09±0.63	4.10±0.48	1.08±0.31	1.29±0.30	3.01±0.39	2.81±0.25	246.1±19.7	218.1±16.4

Clofibrate did not have any effect in the absence of ADH and did not alter the responses to any of the injected amounts of ADH. Figures represent mean ±SEM.

and at 30 mU/100 g of rat on day 3. When the data for the 3 day period after the injection of 30 mU of PTO/100 g were pooled, the clofibrate significantly increased the urine volume and free water clearance. Since ADH exerts its renal action by activating adenyl cyclase and increasing tissue cyclic AMP concentrations (14), it is tempting to speculate that in some way the slight diuretic action of clofibrate might be related to the reported inhibition of adenyl cyclase activity by clofibrate in several tissues (15).

The evidence supports the possibility that clofibrate exerts an antidiuretic action by increasing the release of ADH from the neurohypophysis. Chlorpropamide, which has a similar ADH-like action, may also increase the release of ADH (16), but also augments the peripheral action of ADH in the diabetes insipidus rat (12, 13), perfused dog kidney (17), and the toad bladder (18). The degree of antidiuresis exerted by clofibrate and chlorpropamide was similar in water-loaded normal subjects, but urinary ADH excretion was twice as great with clofibrate (reference 16 and unpublished observations). This could support the concept that the antidiuretic action of clofibrate is through ADH release, while that of chlorpropamide is through ADH release and augmentation of its peripheral action. The difference in antidiuretic mechanism of the two drugs is also a possible explanation for the absence of reports on dilutional hyponatremia in hyperlipidemic patients treated with clofibrate in contrast to the problem of dilutional hyponatremia in patients with diabetes mellitus who are treated with chlorpropamide (19).

Clofibrate and chlorpropamide have in common a chlorinated benzene ring which may conceivably offer a molecular clue to the structure-function relationships of these two drugs. The sulfonylurea drugs tolazamide, acetohexamide, and glibenclamide, do not have an antidiuretic action in water-loaded normal subjects and in fact exert a significant diuretic action, the mechanism of which is as yet unexplained (reference 19 and unpublished observations). Because of the opposite effect of chlorpropamide and the other three sulfonylurea drugs on water excretion it is apparent that the sulfonylurea part of the molecule is not involved in the alteration of water metabolism.

In these experiments, as in previous studies done with chlorpropamide (1), clofibrate has a greater antidiuretic action in water-loaded diabetes insipidus patients than in water-loaded normal subjects (Fig. 1). Two possible explanations for this are that clofibrate and chlorpropamide are more effective in releasing ADH in the water-loaded diabetes insipidus patient than in the normal, or that the water-loaded patient with diabetes insipidus is less able to inhibit ADH release than the normal so that the summation of subantidiuretic amounts of circulating ADH plus additional ADH released by clofibrate and chlorpropamide would result in a greater antidiuresis. Perhaps an analogous situation to the latter possibility is the resistance to dexamethasone suppression of some patients with disease of the anterior pituitary or hypothalamus (20).

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REFERENCES

1. Miller, M., and A. M. Moses. 1970. Mechanism of chlorpropamide action in diabetes insipidus. *J. Clin. Endocrinol. Metab.* **30**: 488.
2. Webster, B., and J. Bain. 1970. Antidiuretic effect and complications of chlorpropamide therapy in diabetes insipidus. *J. Clin. Endocrinol. Metab.* **30**: 215.
3. Uhlich, E., K. Loeschke, J. Eigler, and R. Halbach. 1971. Clofibrat bei diabetes insipidus. *Klin. Wochenschr.* **49**: 436.
4. de Gennes, J.-L., C. Bertrand, B. Bigorie, and J. Truffert. 1970. Études préliminaires de l'action antidiurétique du clofibrate (ou atromid S) dans le diabète insipide pitressosensible. *Ann. Endocrinol.* **31**: 300.
5. de Gennes, J.-L., J.-Cl. Desbois, and J. Marie. 1970. Étude thérapeutique du clofibrate au cours des diabètes insipides pitresso-sensibles de l'enfant. *Ann. Pediatr. (Paris)*. **17**: 754.
6. Miller, M., T. Dalakos, A. M. Moses, H. Fellerman, and D. H. P. Streeten. 1970. Recognition of partial defects in antidiuretic hormone secretion. *Ann. Intern. Med.* **73**: 721.
7. Valtin, H. 1967. Hereditary hypothalamic diabetes insipidus in rats (Brattleboro strain). A useful experimental model. *Am. J. Med.* **42**: 814.
8. Miller, M., and A. M. Moses. 1971. Radioimmunoassay of urinary antidiuretic hormone with application to study of the Brattleboro rat. *Endocrinology.* **88**: 1389.
9. Miller, M., and A. M. Moses. 1972. Radioimmunoassay of urinary antidiuretic hormone in man: response to water load and dehydration in normal subjects. *J. Clin. Endocrinol. Metab.* **34**: 537.
10. Miller, M., and A. M. Moses. 1972. Urinary antidiuretic hormone in polyuric disorders and in inappropriate ADH syndrome. *Ann. Intern. Med.* **77**: 715.
11. Kleeman, C. R., M. E. Rubini, E. Lamdin, and F. H. Epstein. 1955. Studies on alcohol diuresis. II. The evaluation of ethyl alcohol as an inhibitor of the neurohypophysis. *J. Clin. Invest.* **34**: 448.
12. Berndt, W. O., M. Miller, W. M. Kettyle, and H. Valtin. 1970. Potentiation of the antidiuretic effect of vasopressin by chlorpropamide. *Endocrinology.* **86**: 1028.

13. Miller, M., and A. M. Moses. 1970. Potentiation of vasopressin action by chlorpropamide in vivo. *Endocrinology.* **86**: 1024.
14. Robison, G. A., R. W. Butcher, and E. W. Sutherland. 1971. Cyclic AMP. Academic Press Inc., N. Y. 339.
15. Greene, H. L., R. H. Herman, and D. Zakim. 1970. The effect of clofibrate on rat tissue adenyl cyclase. *Proc. Soc. Exp. Biol. Med.* **134**: 1035.
16. Moses, A. M., P. Numann, and M. Miller. 1973. Mechanism of chlorpropamide-induced antidiuresis in man: evidence for release of ADH and enhancement of peripheral action. *Metab. (Clin-Exp).* In press.
17. Zweig, S. M., B. Ettinger, and L. E. Earley. 1971. Mechanism of antidiuretic action of chlorpropamide in the mammalian kidney. *Am. J. Physiol.* **221**: 911.
18. Ingelfinger, J. R., and R. M. Hays. 1969. Evidence that chlorpropamide and vasopressin share a common site of action. *J. Clin. Endocrinol. Metab.* **29**: 738.
19. Garcia, M., M. Miller, and A. M. Moses. 1971. Chlorpropamide-induced water retention in patients with diabetes mellitus. *Ann. Intern. Med.* **75**: 549.
20. Moses, A. M., and M. Miller. 1968. Stimulation and inhibition of ACTH release in patients with pituitary disease. *J. Clin. Endocrinol. Metab.* **28**: 1581.