STUDIES ON ALCOHOL DIURESIS. II. THE EVALUATION OF ETHYL ALCOHOL AS AN INHIBITOR OF THE NEUROHYPOPHYSIS [1, 2]

By CHARLES R. KLEEMAN, MILTON E. RUBINI,[3] EZRA LAMDIN,[4] AND FRANKLIN H. EPSTEIN

(From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.)

(Submitted for publication September 7, 1954; accepted November 24, 1954)

In the normally hydrated semi-recumbent individual, alcohol causes a rise in urine flow that is characterized by an increase of free water clearance (C_{H_2O}) and a decreased excretion of sodium, potassium and chloride (1). The evidence to date strongly suggests that the rise of C_{H_2O} is caused by inhibition of the release of antidiuretic hormone.

The present study was undertaken to evaluate the effect of alcohol on the excretion of water and solutes in physiologic states in which alterations in the activity of antidiuretic hormone have been demonstrated or suggested. The following states were studied: 1) Minimal antidiuretic hormones (ADH) activity produced by sustained positive loads of water; 2) Increased ADH activity produced by infusions of hypertonic sodium chloride solutions, a) during water diuresis with high urine flows (10 to 15 cc. per min.), and b) in subjects with low urine flows (1 to 2 cc. per min.); 3) Increased antidiuretic activity produced by venous congestion of the limbs.

MATERIALS, METHODS AND RESULTS

Subjects were normal males, aged 25 to 32. No control of diet prior to the day of study was attempted. One to one and a half hours after a light breakfast the subjects voided and reclined in a semi-recumbent position. All studies were begun at 8:30 to 9:00 A.M.; diurnal variations in urinary flow and composition (2) were therefore presumably similar in all experiments. Alcohol was given as 120 cc. of 100 proof bourbon whisky imbibed over a 10-minute period. Techniques for collection of blood and urine and chemical methods have been described in the previous paper (1). In all studies insensible water loss was assumed to be approximately 50 cc. per hour. Changes in extracellular space were calculated approximately from changes in the chloride space (3), assuming an initial extracellular volume of 20 per cent of body weight. Changes in plasma volume were calculated from changes in hemoglobin and hematocrit (1). Urine flow was divided into two fractions:

$$\text{Osmolar clearance } (C_{osm}) = \frac{\text{milliosmols per kilo of urine}}{\text{milliosmols per kilo of plasma}} \times \text{urine flow (cc. per min.)}$$

$$\text{Free water clearance } (C_{H_2O}) = \text{urine flow} - C_{osm}$$

Group I. Effect of alcohol during water diuresis (Table I, Figure 1C)

A positive water balance was induced in two semi-recumbent subjects by drinking one liter of water, and was maintained by infusing 4 per cent fructose solution intravenously and administering supplemental water by mouth. The accuracy of this technique was checked by weighing the subject at the beginning and the end of each experiment. Fructose solution was chosen because of its minimal effect on the total hexose in the blood. By limiting the rate of infusion to 8 cc. per minute or less, no reducing substances could be detected in the urine by qualitative test with Benedict's solution. After a maximal steady urine flow had been maintained for at least two 30-minute periods, alcohol was imbibed. Urine was collected at 15 to 30-minute intervals during the next three hours.

Under these circumstances, alcohol did *not* induce a further increase in urine flow or C_{H_2O} (Figure 1C). If large positive loads of water (1000 cc.) completely inhibit ADH release ("physiologic diabetes insipidus"), this result would be expected.[5] The rates of excretion

[1] Supported in part by a Grant from the U. S. Public Health Service.

[2] Presented in abstract form at the meeting of the American Society for Clinical Investigation, Atlantic City, May 2–5, 1954.

[3] Major, MC, USA.

[4] Postdoctorate Research Fellow of the U. S. Public Health Service.

[5] The statement that maximum water diuresis is associated with complete inhibition of ADH release or so-called "physiologic diabetes insipidus" probably is true for the recumbent and semi-recumbent positions only. In unpublished experiments the authors have demonstrated that when a positive water load of 1000 cc. is maintained, the maximum urinary flow and free water clearance (C_{H_2O}) attained in the standing or 45° position were further increased by lying down. This suggests a continual "tonic" release of ADH in the upright positions in spite of the sustained water load or non-hormonal factors blocking the maximum rise in urinary flow.

TABLE I

Group I—1000 cc. positive H_2O load with and without alcohol

Subject	Time	Urine: pH	Urine: Excretion rates/min. Na	K	Cl	NH_3	TA	Osm.*	Vol.	Clearances/min. Osm.	Free	Creat.	Blood: Na	K	Cl	Alc.	pH	Osmolarity Obs.	Corr.*	PV‡/PV†
	Min.	*Units*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μOsm.*	*cc.*	*cc.*	*cc.*	*cc.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg. %*	*Units*	*mOsm./L.*	*mOsm./L.*	*% Δ*
K.	73	6.5	113	79	121	19	4	650	1.6	2.2	−0.6	126	146.7	4.64	105.0			303	303	0
	32	6.1	98	50	110	40	9	945	9.8	3.2	6.6	130								
Exp. 1	30	6.1	88	41	111	36	7	820	10.0	2.8	7.2	121								
	32	6.2	93	41	107	38	7	865	10.3	2.9	7.4	127								
	27	6.3	114	38	107	35	9	880	10.5	3.0	7.5	132	140.6	4.78	99.5			290	290	+5
	31‡	6.2	127	33	129	39	10	890	10.9	3.1	7.8	148	142.1	3.59	101.2			303	288	+17
	28	5.9	120	23	123	37	7	840	10.3	2.9	7.4	145	142.1	3.30	102.5			313	287	+18
	32	5.8	122	19	122	36	7	840	10.2	2.9	7.3	139	142.2	3.07	100.7			314	285	+16
	31	5.8	105	16	98	37	9	785	9.6	2.7	6.9	145								
		6.2	101	14	93	34	8	795	9.7	2.7	7.0	140	142.0	3.49	103.0			312	290	+16
H.	57	6.0	149	49	157	33	11	860	0.6	3.0	−2.4		140.5	4.00	105.5	0	7.38	288	288	
Exp. 2	38	6.9	162	87	180	28	4	900	2.0	3.1	−1.2									
	18	6.6	100	104	133	27	10	1,030	7.8	3.6	4.2	132								
	24	6.6	113	94	117	25	16	1,020	11.3	3.5	7.8	138								
	27	6.3	96	71	94	28	8	930	12.2	3.2	9.0	130								
	46	6.3	72	43	64	28	7	770	9.9	2.7	7.2	121								
	37	6.3	79	38	66	30	8	760	9.7	2.7	7.0	128	137.0	3.90	101.5	0		284	284	
	51‡	6.2	79	32	60	30	16	670	8.8	2.4	6.4	125	138.0	4.12	101.5	105	7.33	306	280	
	43	5.9	87	20	64	31	20	720	9.4	2.6	6.8	136				96				
	40	6.1	89	21	62	31	21	710	9.1	2.5	6.6	136								
	41	6.0	78	21	48	27	19	650	8.2	2.3	5.9	122	137.0	3.92	101.7	70	7.44	301	280	

* Observed osmolarity—osmolar contribution of alcohol. † PV = Plasma volume. ‡ Alcohol imbibed during first 10 minutes of this period.

of Na and Cl did not decrease after alcohol ingestion and although the urine became more acid, excretion of ammonium was not enhanced. These results contrast sharply with the findings when alcohol is administered to subjects with low or moderate urinary flows (1).

Group IIa. Effect of the simultaneous administration of alcohol and hypertonic saline to water-loaded subjects (Table IIA, Figure 1A and 1B)

Positive water balances were achieved in four experiments in a manner similar to that described for Group I. In two control tests (No. 1 and No. 2 Table IIA) 500 cc. of hypertonic saline (5 to 6 per cent) was infused without alcohol. In two further experiments (No. 3 and No. 4, Table IIA), alcohol was imbibed simultaneously with the beginning of the hypertonic infusion.

The administration of hypertonic saline without alcohol, at the height of a water diuresis, was followed by a prompt decrease in urine flow and free water clearance (Figure 1A). In contrast, the subjects receiving alcohol not only failed to show an antidiuresis, but actually *increased* their flow of urine above the levels reached during maximal water diuresis (Figure 1B). Free water clearance (C_{H_2O}) increased in spite of a 4 to 5 per cent rise in the osmolarity of the serum. It is apparent that alcohol effectively blocked the antidiuretic response to hypertonic saline.

Group IIb. Effect of alcohol on the antidiuresis following hypertonic saline in subjects with low urine flows (Table IIB, Figure 2)

In two subjects, 300 cc. of 5 to 6 per cent saline were infused intravenously after a suitable control period. Approximately 30 minutes *after* starting the infusion alcohol was imbibed.

In neither subject did a water diuresis occur after alcohol. *Prior* administration of hypertonic saline, with a consequent increase in the effective osmotic pressure of extracellular fluid, presumably induced the release of increased amounts of ADH from the posterior pituitary (4). Since alcohol affects neither exogenous ADH nor the ability of the tubules to respond to this hormone (5) an excess of circulation ADH probably masked the inhibitory effect of alcohol upon the supraopticohypophyseal system in these experiments.

Group III. Effect of alcohol on the antidiuresis of venous congestion (Table III, Figure 3)

The effect of alcohol on the antidiuresis produced by venous congestion of the limbs was tested in three subjects in whom sphygmomanometer cuffs were inflated about the thighs to a pressure of 70 to 80 mm. Hg. (In all, a positive water load of 500 cc. was established and maintained throughout the experiment.) In two studies (No. 1 and No. 2, Table III) a control period of venous congestion for 30 minutes, instituted after maximal urine flow had been attained, produced a prompt fall in urine flow, C_{H_2O}, and C_{osm}, as well as in the rates of excretion of sodium, potassium, chloride, and creatinine. These

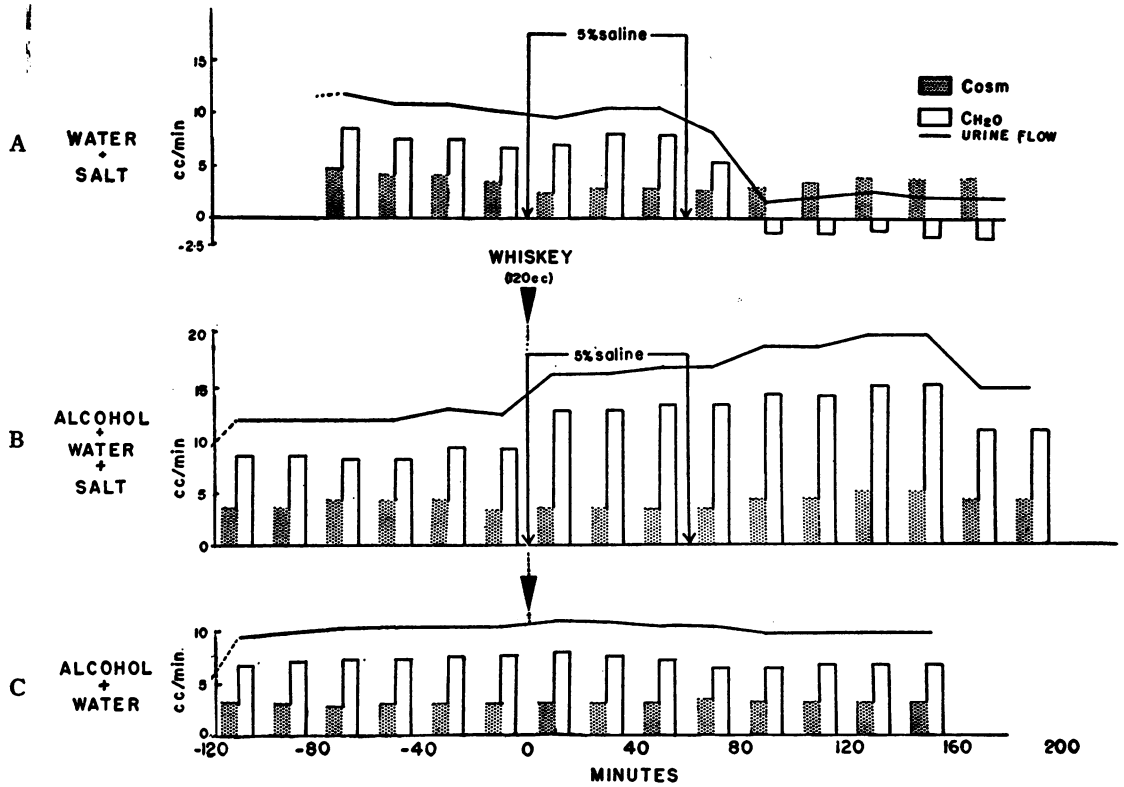

FIGURE 1

Alcohol produced no increase in an established water diuresis (Figure 1C). In contrast, when alcohol was given with an intravenous load of hypertonic saline, urine flow and C_{H_2O} increased (Figure 1B), and the characteristic antidiuretic effect of hypertonic saline (Figure 1A) was blocked.

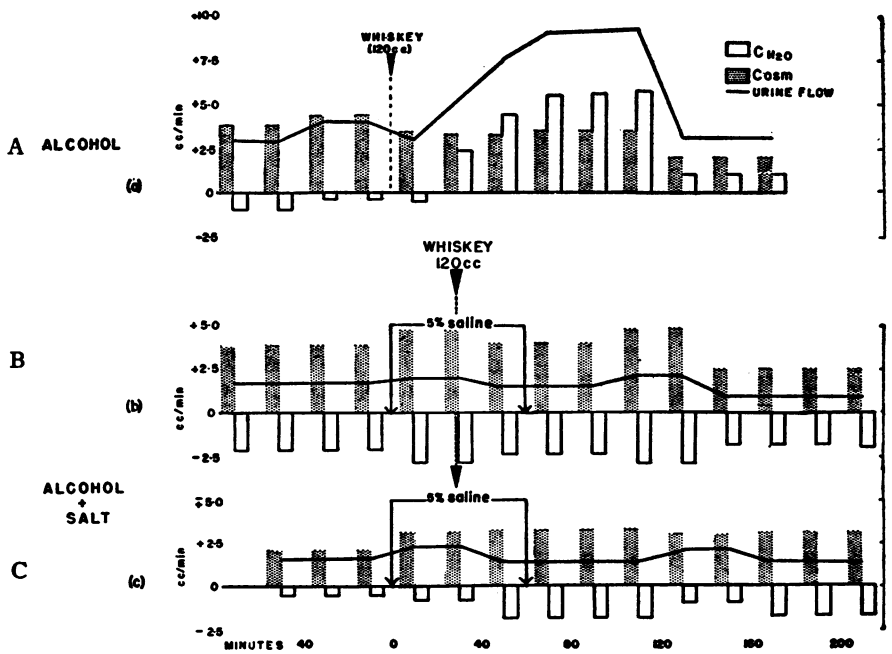

FIGURE 2

Prior administration of hypertonic saline (Figures 2B and 2C) blocked the characteristic diuresis following alcohol (Figure 2A).

TABLE IIA

Group IIa—Hypertonic salt administration with and without alcohol in subjects with maximum water diuresis

		Urine										Blood									
			Excretion rates/min.							Clearances/min.								Osmolarity		$\frac{PV_2}{PV_1}$†	Cl space
Subject	Time	pH	Na	K	Cl	NH_3	TA	Osm.*	Vol.	Osm.	Free	Creat.	Na	K	Cl	CO_2	Alc.	pH	Obs.	Corr.*		
	Min.	*Units*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μOsm.*	*cc.*	*cc.*	*cc.*	*cc.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg. %*	*Units*	*mOsm./L.*	*mOsm./L.*	*% Δ*	*Liters*
Ki.	117	7.0	188	78	169	17			2.3			126	144.7	4.08	108.5				290		0	14.1
	19	6.3	414	147	242	42		1,640	16.5	7.3	9.2	141										
Exp. 1	15	6.4	457	146	222	34		1,660	18.3	7.7	10.6	118										
	17	6.2	415	104	169	45		1,580	19.1	6.8	12.3	123										
	20	5.6	261	78	45	54		1,090	13.2	4.7	8.5	119										
	38	5.5	215	82	49	57		930	11.6	4.1	7.5	121	138.9	4.50	104.2				277		− 8	14.5
	30	5.9	160	61	62	46		855	10.1	3.5	6.6	125										
	20	5.8	132	48	68	57		685	9.5	2.5	7.0	121										
	36]	5.9	181	44	94	42		810	11.0	2.9	8.1	121	142.0	4.30	111.4				289		− 5	15.4
	33]		227	31	194	38		800	8.1	2.7	5.4	119	146.0		114.8				289		0	16.2
	20		295	38	269	35		875	1.6	3.0	−1.4	123										
	24		308	70	311	39		1,005	2.1	3.5	−1.4	128										
	25		334	106	372	38		1,100	2.7	3.8	−1.1	127										
	21		328	120	385	38		1,085	2.1	3.8	−1.7	123										
	26		324	123	371	37		1,110	2.1	3.9	−1.8		143.8	4.15	112.7				288		− 2	16.2
Re.	57	6.6	257	163	328	52	10	1,335	6.8	4.6	2.2	156	143.0	4.59	105.0	25.5		7.46	290		0	
	34	6.8	271	201	361	43	10	1,525	12.9	5.0	7.9	152										
Exp. 2	40	6.2	198	129	147	47	10	1,420	17.1	3.9	13.2	140										
	47	6.5	138	82	124	46	9	1,145	16.8	3.6	13.2	144	139.3	4.38	101.0	23.7		7.37	273		+ 3	
	68]	6.6	197	90	182	39	9	1,320	15.2	3.3	11.9	140										
	46]	6.1	288	86	304	42	7	1,220	11.1	3.4	7.7	138	147.2	4.26	110.4	24.9		7.38	332		+ 8	
	37	6.4	304	122	364	49	8	1,335	11.0	4.2	6.8	142										
	31	6.2	347	122	416	40	8	1,340	9.4	4.6	4.8	139										
	31	6.4	346	125	390	33	8	1,555	11.0	5.2	5.8	145	143.5	4.61	107.6	25.6		7.44	297			
	109	6.2						1,560	4.4	3.2	1.2											
R.	111	7.5	435	205	477	24		1,685	7.1	6.0	1.1	161	133.0	4.20	101.5	27.2	0	7.40	283	283		
	56	7.2	358	163	379	22	1	1,470	6.9	5.2	1.7	155										
Exp. 3	35	6.7	165	89	151	25	4	970	12.0	3.6	8.4	142										
	40	6.3	195	55	84	36	9	1,100	12.0	3.9	8.1	132										
	30	6.3	196	31	64	42	6	1,050	13.0	3.8	9.2	140										
	24	6.3	160	20	68	37	13	885	12.3	3.2	9.1	140	133.0	3.68	100.0	23.4	0	7.30	276	276	+11	14.3
	41]‡	6.6	295	36	194	35	6	990	16.2	3.5	12.7	150	133.9	3.18	108.0	19.4	78		302	286	+21	14.6
	33]	6.6	231	11	165	39	15	970	16.7	3.3	13.4	166	144.8	3.43	113.0	21.5	96	7.26	311	291	+32	14.8
	36	6.5	304	23	188	35	8	1,250	18.7	4.3	14.4	135					182					
	37	6.7	332		180	26	6	1,420	20.0	4.9	15.1	135										
	43	6.2	279	15	138	35	9	1,195	14.9	4.1	10.8	138	135.3	4.20	107.5	22.4	24	7.44	296	292	+24	15.4
R.	65	7.1	174	90	167	22	0	960	3.7	3.1	0.6	117	139.1	4.30	98.5				307	307		15.6
	27	6.6	171	59	126	24	0	1,055	11.1	3.5	7.6	121										
Exp. 4	23	5.5	166	71	75	43	27	1,245	11.5	4.1	7.4	128										
	17	5.3	237	47	61	54	19	1,530	13.8	5.1	8.7	111										
	19	5.3	275	28	85	51	18	1,660	14.5	5.0	9.5	108										
	20	5.2	234	26	73	50	8	1,285	13.3	4.3	9.0	111										
	19	5.5	203	21	93	43	11	1,130	13.7	3.9	9.8	115	139.8	4.32	95.0	24.5		7.39	302	302	+ 4	16.0
	25]‡	5.4	280	28	148	31	7	1,130	14.3	3.7	10.6	109										
	31]	5.5	239	21	177	26	6	1,125	14.8	3.6	11.2	123	145.5	4.10	103.0	23.0		7.41	326	312		16.1
	25]	6.0	309	20	257	23	6	1,335	16.7	4.2	12.5	110										
	20	6.0	332	28	294	25	8	1,375	17.0	4.2	12.8	121	145.3	4.31	103.5	24.1		7.44	340	322		16.9
	18	5.8	513	21	402	16	25	1,625	16.6	5.0	11.6	122										
	17	5.8	616	25	493	37	37	1,740	17.2	5.4	11.8	117										
	21	5.5	452	20	399	35	22	1,405	15.5	4.4	11.1	117	143.3	4.23	105.2	22.5		7.28	338	318	+10	16.5
	20	5.5	526	26	401	36	22	1,555	15.8	4.9	10.9	118										
	21	5.5	535	15	368	45	28	1,570	16.2	5.0	11.2	116	143.3	4.08	105.0	23.0		7.35	332	316		16.3
	30		317	11	263	36	18	1,065	6.7	3.4	3.3											

* Observed osmolarity—osmolar contribution of alcohol.
† PV = Plasma volume.
‡ Alcohol imbibed during first 10 minutes of this period.
] Period of infusion of hypertonic salt.

TABLE IIB

Group IIb—Hypertonic salt and alcohol administration in subjects with low urine flows

Subject	Time	Urine									Blood								
			Excretion rates/min.						Clearances/min.							Osmolarity		PV‡/PV₁	Cl space
		pH	Na	K	Cl	NH_3	TA	Osm.*	Vol.	Osm.	Free	Creat.	Na	K	Cl	CO_2	Alc.	pH	Obs.	Corr.*		
	Min.	*Units*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μOsm.*	*cc.*	*cc.*	*cc.*	*cc.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg. %*	*Units*	*mOsm./L.*	*mOsm./L.*	*% Δ*	*Liters*
K.	65	7.1	142	90	178	13	4	640	1.6	2.1	−0.5	149	136.7	4.18	102.6	27.6	0	7.49	292	292		14.4
	40	7.1	222	104	260	18		915	2.3	3.1	−0.8	132	137.4	4.18	104.9	25.5	0	7.47	298	298	+5	15.1
Exp. 1	75 ‡	5.5	295	90	358	23	21	1,010	1.4	3.3	−1.9	140	143.5	3.90	109.7	23.9	106	7.27	328	309	+15	15.3
	32	5.1	234	83	296	28	24	960	2.1	3.0	−0.9	133	141.0	4.46	109.5	26.0	128	7.33	325	314	+10	15.2
	77	5.4	280	90	329	24	27	1,000	1.4	3.3	−1.9	148	141.5	4.49	109.1	25.9	62	7.42	322	310	+16	15.1
L.	81	7.4	249	142	298	20	0	1,025	1.7	3.8	−2.1	122	137.6	3.98	101.5	25.7		7.41	268			17.0
	38	7.5	341	168	438	22	0	1,310	2.0	4.7	−2.7	121	141.6	4.04	105.2	25.0		7.45	278		+6	17.3
Exp. 2	52 ‡	6.8	408	117	510	24	2	1,210	1.5	4.1	−2.6	127	144.1	3.98	105.5	22.5	80	7.34	311	290	+14	18.2
	40	6.0	402	118	500	33	15	1,430	2.1	5.1	−3.0	132	143.0	4.16	105.0	23.0	96	7.43	299	274		18.1
	50	5.0	203	92	281	26	29	795	0.9	2.8	−1.9	126	141.6	4.30	104.2	22.8	74	7.41	295	275	+12	18.1
	63	5.7	223	62	241	25	31	820	0.9	2.9	−2.0	128	140.5	4.30	103.0	24.7	48	7.43	288	274		18.2

* Observed osmolarity—osmolar contribution of alcohol.
† PV = Plasma volume.
‡ Alcohol imbibed during first 10 minutes of this period.
] Period of infusion of hypertonic salt.

functions returned to or toward control levels after the congestion was released. After a suitable period of recovery, during which the urine flow stabilized, alcohol was administered 30 minutes prior to the application of congesting cuffs for the second time, this time for 60 minutes. Despite a more prolonged period of venous congestion, only slight falls in urine flow and free water clearance were produced, although the decrease in solute excretion and C_{osm} was comparable to that during the control period of cuffing. Under these circumstances, therefore, *prior* ingestion of alcohol minimized the antidiuretic effect of venous congestion (Figure 3A).

In a third subject (No. 3, Table III), alcohol was imbibed 100 minutes *after* the cuffs had been inflated. Urine flow and C_{H_2O}, which had diminished after the cuffs had been applied, did *not* increase after alcohol was administered, and started to rise only after the cuffs were released (Figure 3B).

DISCUSSION

In the present study, alcohol prevented or minimized the fall of urine flow and free water clearance (C_{H_2O}) that characteristically follows the administration of hypertonic solutions of sodium chloride or venous congestion of the extremities. Alcohol will also prevent the antidiuresis of dehydration (6) or the administration of acetylcholine (7) and nicotine (6), and it has no effect on urine flow when it is given at the height of water diuresis or to dogs with diabetes insipidus (7). These observations constitute overwhelming evidence that it has an inhibitory action on the supraopticohypophyseal system.

The antidiuresis that regularly follows venous congestion of the lower extremities or stationary standing has been ascribed in part to increased activity of the neurohypophysis as a result of diminished effective blood volume (8, 9). Facts in favor of this interpretation are: 1) a diminished or absent response in subjects with diabetes insipidus or in hydropenic subjects with maximal ADH activity who are undergoing a mannitol diuresis (10); 2) a fall in urine flow out of proportion to the changes in electrolyte excretion and glomerular filtration (8, 9); 3) the appearance of an antidiuretic substance in the blood of normal subjects after circulatory collapse induced by motionless standing (11). The ability of alcohol to inhibit the antidiuresis of venous congestion lends added weight to the concept that changes in urine flow following alterations in the volume and distribution of body fluids are to an important degree

TABLE III

Group III—Venous congestion of the lower extremities with and without alcohol

Subject	Time	Urine: pH	Urine: Excretion rates/min. Na	K	Cl	NH_3	TA	Osm.*	Vol.	Urine: Clearances/min. Osm.	Free	Creat.	Blood: Na	K	Cl	CO_2	Alc.	pH	Osmolarity Obs.	Corr.*	PV_2† / PV_1
	Min.	*Units*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μEq.*	*μOsm.*	*cc.*	*cc.*	*cc.*	*cc.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg. %*	*Units*	*mOsm./L.*	*mOsm./L.*	*% Δ*
N.	76	6.8	241	148	226	20		984	1.4	3.5	−2.1	166	140.0	4.10	105.3		0		280	280	0
	37	7.0		39	168	32		880	12.4	3.2	9.2	164									
Exp. 1	26	6.8	196	62	170	23		955	16.0	3.5	12.5	160									
	21	6.9	210	57	173	31		1,000	20.0	3.7	16.3	162	140.6	4.21	104.0		0		275	275	
	36]	6.9	167	42	153	23		820	8.0	3.0	5.0	159	138.0	4.05	103.3		0		272	272	+ 5
	46	6.7	145	30	88	24		675	9.6	2.5	7.1	130									
	22	6.7	211	45	141	31		1,010	20.7	3.7	17.0	184									
	17	6.7	219	41	146	29		1,000	19.4	3.7	15.7	179									
	20	6.8	228	39	152	28		1,060	20.8	3.9	16.9	173									
	25‡	6.9	236	37	160	27		915	19.0	3.4	15.6	145									
	25	7.0	248	31	174	20		932	19.4	3.5	15.9	147	132.8	4.00	102.7		58		274	263	+ 3
	28]	6.3	161	22	111	51		720	15.0	2.7	12.3	146									
	36]	6.4	168	24	120	61		845	17.6	3.2	14.4	133	131.8	4.20	102.3				282	260	
	26	6.5	115	18	114	65		810	16.9	3.1	13.8	130									
	20	6.6	107	19	88	18		730	15.2	2.8	12.4	134					80				
	20	6.6	122	20	91	22		825	17.2	3.1	14.1	137	138.6	4.20	104.8		68		286	267	+ 8
W.	65	6.8	245	219	314	31		1,230	6.6	4.4	2.2	160	139.4	3.70	103.7		0		280	280	0
	47		268	123	298	26		1,190	13.2	5.3	7.9	168									
Exp. 2	26		342	152	392	33		1,480	16.8	5.4	11.4	166									
	35	6.6	350	171	399			1,650	17.5	6.1	11.4	162	134.8	4.45	102.0		0		270	270	
	32]	6.5	221	108	274	33		1,060	10.9	3.9	7.0	151	134.5	4.30	100.2		0		273	273	+17
	42	6.3	178	75	204	35		870	9.6	3.2	6.4	131									
	64	6.5	189	63	204	30		816	8.9	3.0	5.9	148									
	23‡	6.7	273	89	288	31		1,015	11.3	4.1	7.2	155									
	21	6.6	274	63	271	33		940	11.0	4.0	7.0	151									
	32]	6.9	222	44	222	37		750	8.9	2.9	6.0	122	130.8	4.00	99.2		80		276	258	+16
	31]	6.2	222	32	225	40		770	8.9	3.0	5.9	145					120				
	32	6.0	191	19	184	46		700	8.1	2.7	5.4	140	130.8	3.82	99.0		92		285	260	+ 9
	38	6.1	194	25	186	33		845	9.4	3.2	6.2	158									
	31	6.2	171	16	156	34		825	9.8	3.1	6.7	166	132.5	3.50	99.2		44		284	266	+17
S.	65	6.6	175	79	179	20	6	905	1.2	3.1	−1.9	145	145.6	3.96	105.8	26.9	0	7.38	292	292	0
	34	6.9	267	146	278	26	8	1,300	8.1	4.5	3.6	124									
Exp. 3	21	6.9	287	164	290	25	12	1,430	14.8	5.0	9.8										
	19	6.8	332	174	333	22	16	1,575	17.9	5.5	12.4	129									
	20	6.7	345	185	354	25	21	1,615	19.7	5.6	14.1	133									
	18	6.7	356	181	365	24	21	1,615	20.3	5.6	14.7	134									
	24]	6.6	289	154	290	30	27	1,395	18.1	4.9	13.2	122	138.7	4.30	102.6	27.0	0	7.38	285	285	− 5
	17	6.5	256	141	262	31	30	1,305	17.6	4.6	13.0	131									
	18	6.3	199	113	204	33	26	1,115	15.9	3.9	12.0	134									
	22	6.3	185	106	185	35	28	1,065	15.4	3.7	11.7	141									
	18	6.3	173	88	162	33	31	1,035	15.0	3.5	11.5	145							289	287	
	20 ‡	6.2	168	78	139	38	31	1,028	14.2	2.9	11.3	143									
	21	5.4	162	50	97	28	33	815	10.5	2.6	7.9	127	140.5	4.00	102.2	19.8	104	7.16	309	288	− 7
	20	5.5	152	44	94	27	33	745	10.5	2.8	7.7	134					118				
	20	5.6	110	28	66	28	34	800	10.8	2.6	8.2	139									
	22]	5.6	106	21	65	27	33	740	10.9	2.5	8.4	131									
	17	5.6	88	24	45	28	33	720	10.6	2.5	8.1	139					96				
	21	5.6	94	21	48	30	29	740	11.2	2.6	8.6	143									
	20	5.8	92	20	48	28	31	720	11.3	2.5	8.8	134									
	20	5.9	112	20	54	26	32	750	12.5	2.6	9.9	139	141.4	3.90	100.8	24.8	40	7.41	312	302	− 3
	20	6.0	122	21	62	24	29	755	13.0	2.6	10.4	136									
	20	6.9	133	22	75	28	32	755	14.0	2.6	11.4	141									

* Observed osmolarity—osmolar contribution of alcohol.
† PV = Plasma volume.
‡ Alcohol imbibed during first 10 minutes of this period.
] Period venous congestion.

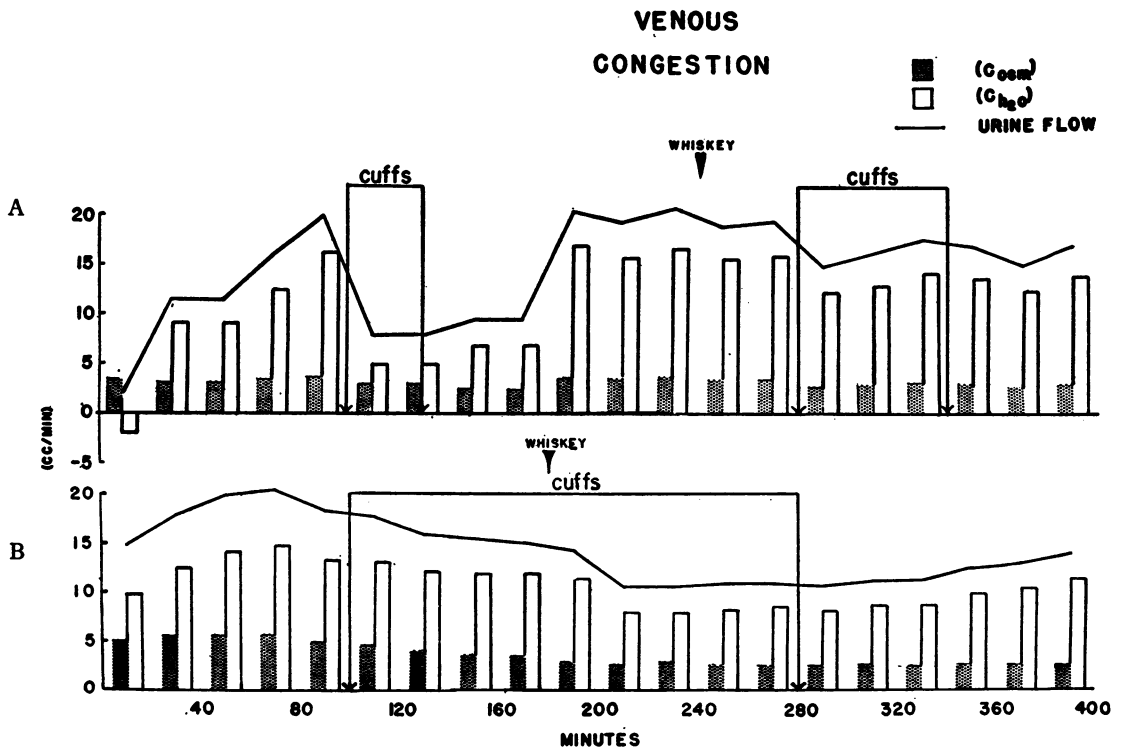

FIGURE 3

Alcohol minimized the antidiuretic effect of venous congestion when given *prior* to the latter (Figure 3A). In contrast, alcohol had little effect when given *during* the period of venous congestion (Figure 3B).

secondary to variations in the activity of the neurohypophysis.[6]

Alcohol had little effect on urine flow and free water clearance in those experiments in which it was given *after* an infusion of hypertonic saline or venous congestion had been initiated. Once the neurohypophysis has been stimulated the resultant excess of circulating antidiuretic hormones might, until it is inactivated or destroyed, mask the temporary inhibition of the posterior pituitary by alcohol. These experiments suggest that alcohol diuresis may be blocked by a prior rise in circulating endogenous ADH as well as by the administration of exogenous Pitressin® (5, 6).

In the experiments of Group I, when the release of ADH was presumably completely inhibited by a positive water load in the semi-recumbent position, administration of alcohol caused no further rise in urine flow and free water clearance. The increase in C_{H_2O} which occurred in the water-loaded subjects of Group IIb, to whom alcohol was given simultaneously with an infusion of hypertonic saline, was therefore unexpected. The situation in these experiments is probably comparable to the rapid administration of large solute loads to patients with diabetes insipidus, in whom an increased volume of isosmotic fluid is suddenly delivered to a distal tubular segment in which water reabsorption is blocked but where further reabsorption of solute does occur. In this case an increase in the calculated value of free water clearance (C_{H_2O}) might be produced, not by diminished reabsorption of water in the distal tubule (Smith, 13), but by an increased distal reabsorption of solute. An increase in C_{H_2O} during mannitol or solute diuresis in subjects with diabetes insipidus can in fact be demonstrated by recalculating the data of Brodsky and Rapoport (14). Similar increases in C_{H_2O}, C_{osm}, and urine flow were shown by Welt, Young, Thorup, and Burnett (15) to follow the adminis-

[6] In a study published since completion of this paper Newman (12) demonstrated that alcohol could effectively block the antidiuresis of quiet standing.

tration of a carbonic anhydrase inhibitor to water-loaded subjects who were in a state of "physiological diabetes insipidus." Although tubular secretion of water (14) could explain such changes, there seems little reason to invoke such a concept.

A relative or absolute increase in antidiuretic hormone has been implicated in the abnormal water metabolism of such clinical states as hyponatremia, cirrhosis of the liver, congestive heart failure, adrenal insufficiency, and panhypopituitarism. The results of the present and previous studies (1, 5) suggest that the effects of alcohol in states of abnormal water metabolism might be of value in interpreting their pathophysiology. Such investigations are now in progress.

SUMMARY

1. Alcohol had no effect upon urine flow or solute excretion when given at the height of a water diuresis.

2. Alcohol blocked the antidiuretic response to hypertonic saline when both were simultaneously administered to water-loaded subjects.

3. Alcohol minimized the antidiuretic effect of venous congestion of the legs in water-loaded subjects, when imbibed before the legs were congested.

4. The characteristic diuretic response to alcohol was blocked by prior infusion of hypertonic saline or cuff congestion of the limbs.

5. When administered prior to the stimulus, alcohol will effectively block stimulation of the release of ADH.

ACKNOWLEDGMENT

The authors wish to thank Dr. John P. Peters for his advice and criticism and Drs. D. Lester and L. J. Greenberg of the Department of Applied Physiology, Yale University for their suggestions and assistance in setting up the technique for alcohol determination in the blood. The technical assistance of Mrs. M. Browning and Mrs. M. Kompare is gratefully acknowledged.

REFERENCES

1. Rubini, M. E., Kleeman, C. R., and Lamdin, E., Studies on alcohol diuresis. I. The effect of ethyl alcohol ingestion on water, electrolyte and acid-base metabolism. J. Clin. Invest., 1955, **34**, 439.
2. Stanbury, S. W., and Thomson, A. E., Diurnal variation in electrolyte excretion. Clin. Sc., 1951, **10**, 267.
3. Elkinton, J. R., and Taffel, M., Prolonged water deprivation in the dog. J. Clin. Invest., 1942, **21**, 787.
4. Verney, E. B., The antidiuretic hormone and the factors which determine its release. Proc. Roy. Soc., London, s. B., 1947, **135**, 25.
5. Strauss, M. B., Rosenbaum, J. D., and Nelson, W. P., III, The effect of alcohol on the renal excretion of water and electrolyte. J. Clin. Invest., 1950, **29**, 1053.
6. Eggleton, M. G., The diuretic action of alcohol in man. J. Physiol., 1942, **101**, 172.
7. van Dyke, H. B., and Ames, R. G., Alcohol diuresis. Acta Endocrinol., 1951, **7**, 110.
8. Wilkins, R. W., Tinsley, C. M., Culbertson, J. W., Burrows, B. A., Judson, W. E., and Burnett, C. H., The effects of venous congestion of the limbs upon renal clearances and the excretion of water and salt. I. Studies in normal subjects and in hypertensive patients before and after splanchnicectomy. J. Clin. Invest., 1953, **32**, 1101.
9. Fitzhugh, F. W., Jr., McWhorter, R. L., Jr., Estes, E. H., Jr., Warren, J. V., and Merrill, A. J., The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects. J. Clin. Invest., 1953, **32**, 1163.
10. Judson, W. E., Epstein, F. H., Tinsley, C. M., Burrows, B. A., and Wilkins, R. W., The hemodynamics and renal functional effects of venous congestion of the limbs in patients with diabetes insipidus. J. Clin. Invest., 1950, **29**, 826.
11. Brun, C., Knudsen, E. O. E., and Raaschou, F., On the cause of post-syncopal oliguria. Acta med. Scandinav., 1945, **122**, 486.
12. Newman, E. V., Metabolic adjustments to normal and disturbed circulation in man. New England J. Med., 1954, **250**, 347.
13. Smith, H. W., The Kidney, Structure and Function in Health and Disease. New York, Oxford University Press, 1951.
14. Brodsky, W. A., and Rapoport, S., The mechanism of polyuria of diabetes insipidus in man. The effect of osmotic loading. J. Clin. Invest., 1951, **30**, 282.
15. Welt, L. G., Young, D. T., Thorup, O. A., Jr., and Burnett, C. H., Renal tubular phenomena under the influence of a carbonic anhydrase inhibitor. Am. J. Med., 1954, **16**, 612.