

THE MECHANISM OF ANTIDIURESIS ASSOCIATED WITH THE ADMINISTRATION OF HYDROCHLOROTHIAZIDE TO PATIENTS WITH VASOPRESSIN-RESISTANT DIABETES INSIPIDUS

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TIENTS WITH VASOPRESSIN-RESISTANT DIABETES
INSIPIDUS *

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Laragh, Heinemann, and Demartini first reported that the administration of chlorothiazide during water diuresis results in an increased rate of solute excretion without significant changes in the rate of urine flow (1, 2). This effect was interpreted as indicating that the drug interferes with solute (sodium) reabsorption in the distal portions of the nephron where urinary dilution occurs. Similar evidence supporting the concept that chlorothiazide impairs sodium reabsorption at diluting sites in the distal convolution has been presented elsewhere (3). Such a site of inhibition of sodium reabsorption readily accounts for the increased urinary osmolality observed when thiazide derivatives are administered acutely.¹ Crawford and Kennedy, however, observed that the chronic administration of thiazide derivatives to animals with pituitary diabetes insipidus, and to patients with pituitary or nephrogenic diabetes insipidus, results in a striking diminution in urinary volume as well as an increased urinary osmolality (5). The latter observations have been

repeatedly confirmed (6-13), and the thiazide derivatives have now attained a place of therapeutic usefulness in patients with vasopressin-resistant diabetes insipidus (13).

Inhibition of solute reabsorption in the distal nephron alone does not account for the antidiuretic effect of the thiazide derivatives. As indicated above, such inhibition of solute reabsorption would merely increase urinary osmolality without affecting urinary volume. Therefore, the mechanism whereby volume is reduced must reside in some other direct or indirect action of these agents. The results of the present studies are consistent with the view that the antidiuretic effect of hydrochlorothiazide is a consequence of the losses of sodium induced by the agent and is not due to any unique property of the thiazide derivatives. The antidiuresis is enhanced by a low sodium intake, is diminished by a high sodium intake, and may also be produced by mercurial diuretics, despite apparent differences in the site and mode of action of the latter agents.

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¹ According to Wesson and Anslow (4), the final urine may be considered to be composed of two hypothetical moieties: solute-free water (C_{H_2O}) and an isosmotic portion (C_{OSM}) equal to

$$\frac{(\text{urine osmolality}) (\text{volume})}{(\text{plasma osmolality})}$$

Volume = $C_{H_2O} + C_{OSM}$. During water diuresis, chlorothiazide increases solute excretion (C_{OSM}) without appreciably affecting urine volume. Consequently, one observes a rise in urine osmolality and a fall in C_{H_2O} . From these relationships it has been concluded that this agent interferes with solute (sodium) reabsorption in portions of the nephron where dilute urine is produced by the reabsorption of solute without water (1, 3).

METHODS

Multiple studies were performed on four hospitalized male subjects with vasopressin-resistant diabetes insipidus, ranging in age from seven to seventeen years. Two were brothers, a third had an affected brother, and all had a history of polyuria and polydipsia dating from infancy. Maximal urine osmolalities after a 17- to 20-hour thirst were less than 100 mOsm per kg in three subjects, and not greater than 130 mOsm per kg in one subject (S. Z.). None of the four subjects demonstrated any increase in urinary concentration when dehydration was followed by the administration of vasopressin. All were free of other renal functional abnormalities. The intakes of sodium were controlled by the addition of weighed amounts of sodium chloride to a standard diet containing 9 mEq of sodium. In all instances in which the effects of hydrochlorothiazide were studied, the drug was administered orally, 25 mg every 8 hours. A mini-

TABLE I
Relationship between dietary sodium and the antidiuretic response to hydrochlorothiazide

Dietary sodium	Control*		Hydrochlorothiazide*	
	Urine volume	Urine concentration	Urine volume	Urine concentration
	L/24 hr	mOsm/kg	L/24 hr	mOsm/kg
J.W.				
85 mEq	9.0	74	7.2	108
9 mEq	5.9	63	3.6	121
R.W.				
85 mEq	11.1	66	7.8	109
9 mEq	6.5	57	4.4	111
D.M.				
85 mEq	8.6	95	6.0	130
50 mEq	7.0	73	3.8	175

* Mean values for four days preceding and four days following the initiation of hydrochlorothiazide. The first day of therapy was not included in the calculations.

num of 3 control days preceded each period during which the drug was studied. Except during acute measurements of renal clearance, all determinations on urine were performed on aliquots of 24-hour collections.

Sodium and potassium were determined by internal standard flame photometry. Chloride was determined by amperometric titration (14), and urea and ammonia by the microdiffusion technique of Conway (15). Osmolality was measured cryoscopically (16), and inulin by the method of Walser, Davidson, and Orloff (17).

RESULTS

Influence of dietary sodium on the antidiuretic response to hydrochlorothiazide. Three subjects were studied at two different levels of dietary sodium. The means of urine volume and osmolality for 4 control and 4 experimental days are shown in Table I. Although hydrochlorothiazide resulted in a clear fall in urine volume and a rise in urine osmolality at each level of dietary sodium, the antidiuretic effect was relatively greater when the patient was receiving the diet of lower sodium content. Daily values for urine volume and osmolality of one subject at two levels of dietary sodium are shown in Figure 1. The lower intake of sodium chloride permitted a greater increase in urine osmolality and a relatively greater fall in urine volume during the administration of hydrochlorothiazide. While the patient was on an intake of 9 mEq of sodium, the administration of the drug resulted in a reduction in urine volume which was maintained well below control days throughout the period of therapy (Figure 1, right side). In con-

trast, when he was on an intake of 85 mEq of sodium (Figure 1, left side) urine volumes were not depressed to the same extent during the administration of hydrochlorothiazide, and on same days of therapy the volumes were as great as during the control period. Despite this limited depression of urine volume in the presence of the higher intake of sodium, the urine osmolality remained greater than control values, indicating a continued effect of the drug on distal tubular solute reabsorption (3).

That the continued presence of hydrochlorothiazide is not necessary for persistence of the antidiuretic effect is demonstrated in Tables II and III. In one subject on a sodium restricted diet (Table II) a single 25 mg dose of hydrochloro-

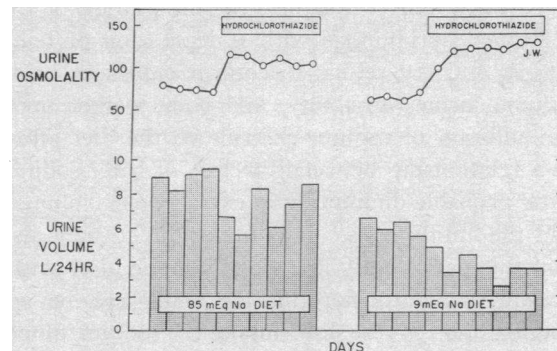


FIG. 1. EFFECT OF DIETARY SODIUM ON ANTIDIURETIC RESPONSE TO HYDROCHLOROTHIAZIDE. Studies were done at an interval of 2 months. Days indicates consecutive days during each study.

TABLE II
Effect of a single injection of hydrochlorothiazide on urinary volume and concentration of Subject R. W. on a 9 mEq sodium diet

Day	Urine			Body weight kg
	Volume L/24 hrs	Osmolality mEq/L	Sodium mEq/24 hrs	
1	6.71	57	3	53.5
2	7.90	56	5	52.9
3	5.82	58	4	53.5
4	6.59	60	2	53.4
Hydrochlorothiazide,* 25 mg i.v.				
5†				
6	3.96	92	9	52.9
7	3.00	97	1	52.5
8	5.33	81	0	52.8
9	3.39	91	1	52.5

* Esidrix.

† Urine collection on day 5 incomplete; values for this day omitted.

thiazide resulted in a fall in urine volume and a rise in urine osmolality that persisted through four days of observation. This persistent antidiuresis was studied further in two additional subjects (Table III). When added sodium was eliminated from the diet prior to discontinuing hydrochlorothiazide, the antidiuresis persisted for several days after withdrawal of the drug. Urine volume and osmolality promptly returned to control levels when sodium chloride was added to the diet. That this persistent antidiuresis after withdrawal of hydrochlorothiazide was related to the lack of sodium intake and not to a cumulative effect of the drug is suggested by the observation that in each subject, recovery from the antidiuresis was evident on the first day and complete by the third day after cessation of therapy with hydrochlorothiazide when the intake of sodium was 50 to 85 mEq daily. Further, the association of the continued antidiuresis with a depression of body weight and the return to control values of urine volume, urine osmolality, and body weight upon the addition of sodium chloride to the diet attest to a relationship between the loss of body sodium (and probable diminution in extracellular volume) and the antidiuresis. It is important to note also that this persistently low urine volume after withdrawal of hydrochlorothiazide could not be accounted for by the low intake of sodium alone, when the values observed in subjects D. M. and S. Z. after hydrochlorothiazide (Table III) were compared to the values observed in the same subjects on a sodium restricted diet alone.

The foregoing observations demonstrate that the reduction in urinary volume incident to the administration of hydrochlorothiazide bears a direct relationship to the dietary intake of sodium. It is demonstrated further that this antidiuretic effect is associated with a maintained deficit of sodium and reduction in body weight. It appears clear that the continued administration of hydrochlorothiazide is not necessary for continuation of the antidiuresis if repair of the sodium deficit is prevented by a rigidly restricted dietary intake.

Antidiuresis after mercurial diuresis. In order to demonstrate further that the antidiuresis is related to the loss of sodium and not to a specific property of the thiazides, the effects of sodium loss secondary to a mercurial diuretic were examined. Two subjects maintained on a daily intake of 9 mEq of sodium were given 40 mg of mercury intramuscularly as mercaptomerin on each of two consecutive days. In both subjects diminished urinary volumes of increased osmolality followed the sodium loss produced by the mercurial. This response in one subject is demonstrated in Figure 2. As shown, the mercurial diuretic resulted in an increased excretion of sodium which was followed by significantly lower urine volumes of increased osmolality. As indicated on the last day shown, an infusion of sodium chloride (70 mEq) resulted in an immediate increase in urine volume and a fall in urine os-

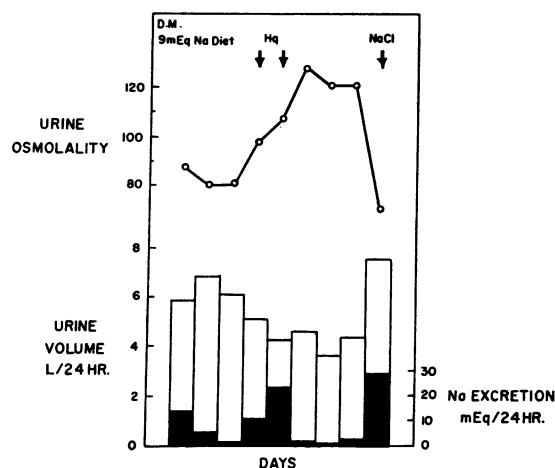


FIG. 2. EFFECT OF SODIUM LOSS FROM MERCAPTOMERIN ON URINARY VOLUME AND CONCENTRATION. *Hg* indicates 40 mg of mercury intramuscularly as mercaptomerin on each of 2 consecutive days. *NaCl* indicates an infusion of 70 mEq of sodium as isotonic saline (see text).

TABLE III
Effect of sodium intake on recovery from antidiuresis induced by hydrochlorothiazide

Subject	Day*	Sodium intake <i>mEq/24 hrs</i>	Urine			Body weight <i>kg</i>
			Volume <i>L/24 hr</i>	Osmolality <i>mOsm/kg</i>	Sodium <i>mEq/24 hrs</i>	
D.M.	3	50	6.85	74	21	24.8
	4	50	7.59	78	37	25.4
	5	50	9.35	68	59	25.1
Hydrochlorothiazide begun, 25 mg every 8 hours						
	6	50	7.07	86	117	25.2
	8	50	4.29	185	70	24.4
	10	50	3.32	185	47	24.3
	12†	50	3.95	181	113	23.8
	13†	50	4.39	161	112	23.8
	14	50	3.41	167	55	23.3
	16	9	3.12	182	2	23.8
	18	9	4.48	166	4	23.6
	20	9	3.99	167	2	23.4
	22	9	3.40	155	2	24.0
Hydrochlorothiazide discontinued						
	23	9	3.44	151	1	23.2
	25	9	3.52	139	2	23.9
	27	9	3.98	120	1	23.7
	28	9	4.60	131	1	23.8
	29	100	7.47	93	9	24.2
	30	50	9.39	68	20	25.0
	32	50	9.96	73	66	24.9
	34	50	8.53	71	60	24.8
S.Z.	3	50	3.64	112	38	24.6
	4	50	4.74	91	47	24.9
	5	50	4.59	95	56	25.1
Hydrochlorothiazide begun, 25 mg every 8 hours						
	6	50	4.04	110	80	25.0
	8	50	2.80	174	46	24.5
	10	50	3.45	171	46	23.9
	12†	50	2.94	164	91	24.0
	13†	50	2.59	165	81	23.6
	14	50	2.58	179	46	23.3
	16	9	3.11	192	4	23.2
	18	9	3.00	174	1	23.2
	20	9	2.36	176	1	23.7
	22	9	2.90	173	1	23.7
Hydrochlorothiazide discontinued						
	23	9	2.39	176	1	23.8
	25	9	2.68	165	1	23.8
	27	9	3.50	153	0	23.9
	28	9	2.59	151	1	23.7
	29	100	4.91	125	2	24.0
	30	50	5.87	92	8	24.6

* Days when therapy and observations were essentially unchanged from preceding day are omitted from table.

† Aldactone, 200 mg, given orally every 8 hours for two days in each study.

molality. Although the antidiuretic response after mercurial diuresis was not so marked as that seen during the continuous administration of hydrochlorothiazide, the losses of sodium in the two subjects who were given mercury were 23 and 29 mEq, respectively, whereas sodium losses during

the administration of hydrochlorothiazide ranged from 75 to 140 mEq.

Effects of a sodium-retaining steroid. As indicated, the above data are consistent with the view that the antidiuretic effect of these diuretic agents is in some way related to a loss of sodium from

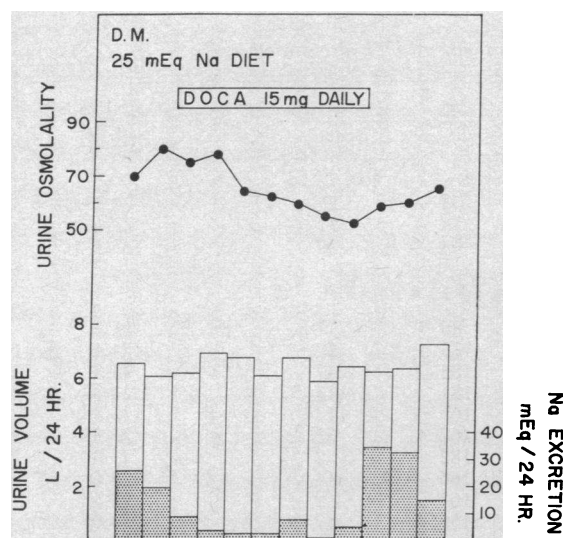


FIG. 3. EFFECT OF SODIUM-RETAINING STEROID ON URINARY VOLUME AND CONCENTRATION. Failure of sodium-retaining steroid to mimic antidiuresis of hydrochlorothiazide. Consecutive days of study are shown. Open bars denote urine volume, stipled area denotes sodium excretion.

the body. Since sodium depletion and the attendant contraction of extracellular volume may result in an increased release of aldosterone (18, 19), the possibility was investigated that the antidiuresis may be mediated through the action of endogenous mineralocorticoid. Desoxycorticosterone acetate (DOCA), 15 mg daily, was given intramuscularly for 7 days to two subjects receiving a diet containing 25 mEq of sodium. In

view of the absence of sodium depletion under the conditions of this study, it was possible to examine the uncomplicated effects of large amounts of the steroid on urinary volume and osmolality. The results of one of these studies are shown in Figure 3. In both subjects, DOCA resulted in a fall in the excretion of sodium to levels below the dietary intake, and when the steroid was discontinued, a sodium diuresis ensued, indicating that a renal effect of the steroid was achieved. Urinary volumes were unchanged during administration of DOCA, and urine osmolality actually fell slightly (as much as 13 mOsm per kg below the range of control values). Thus, the sodium-retaining steroid in no way reproduced the urinary changes associated with the thiazide therapy.

Effects of hydrochlorothiazide on urinary electrolyte composition. Beginning on the first day of therapy, hydrochlorothiazide uniformly resulted in an increased excretion of sodium and, to a lesser extent, potassium. After the first day of therapy the excretion of sodium decreased, and by the fourth to sixth day the output of sodium as well as potassium had returned to control levels (Table IV). These changes in electrolyte excretion are similar to those described by other investigators (20, 21). The total concentration of electrolytes in the urine was immediately increased by hydrochlorothiazide and changed little after the second day of therapy (Figure 4); rather, the return toward control of urinary electrolyte excretion was associated with a diminution in uri-

TABLE IV
Effects of the continuous administration of hydrochlorothiazide to subject (J.W.)
on a daily intake of 9 mEq sodium

Day	Urine				Plasma		Fluid intake L/24 hr	Body weight kg
	Volume	Osmolality	Sodium	Potassium	Urea Nitrogen	Creatinine		
	L/24 hrs	mOsm/kg	mEq/24 hrs	mEq/24 hrs	mg/100 ml	mg/100 ml		
1	5.2	60	5	44	10	0.8	7.3	38.4
2	6.7	61	6	50			6.2	38.9
3	6.4	61	3	48	9	0.8	7.4	39.1
4	5.4	70	5	40			6.4	39.2
Hydrochlorothiazide, 25 mg every 8 hours								
5	4.9	97	57	82			6.0	38.4
6	3.4	118	32	59	12	0.8	5.7	38.3
7	4.6	122	35	91			5.1	38.3
8	3.8	123	17	61			5.0	38.2
9	2.6	120	12	44	17	0.8	3.5	37.8
10	2.5	127	5	32			3.6	37.8

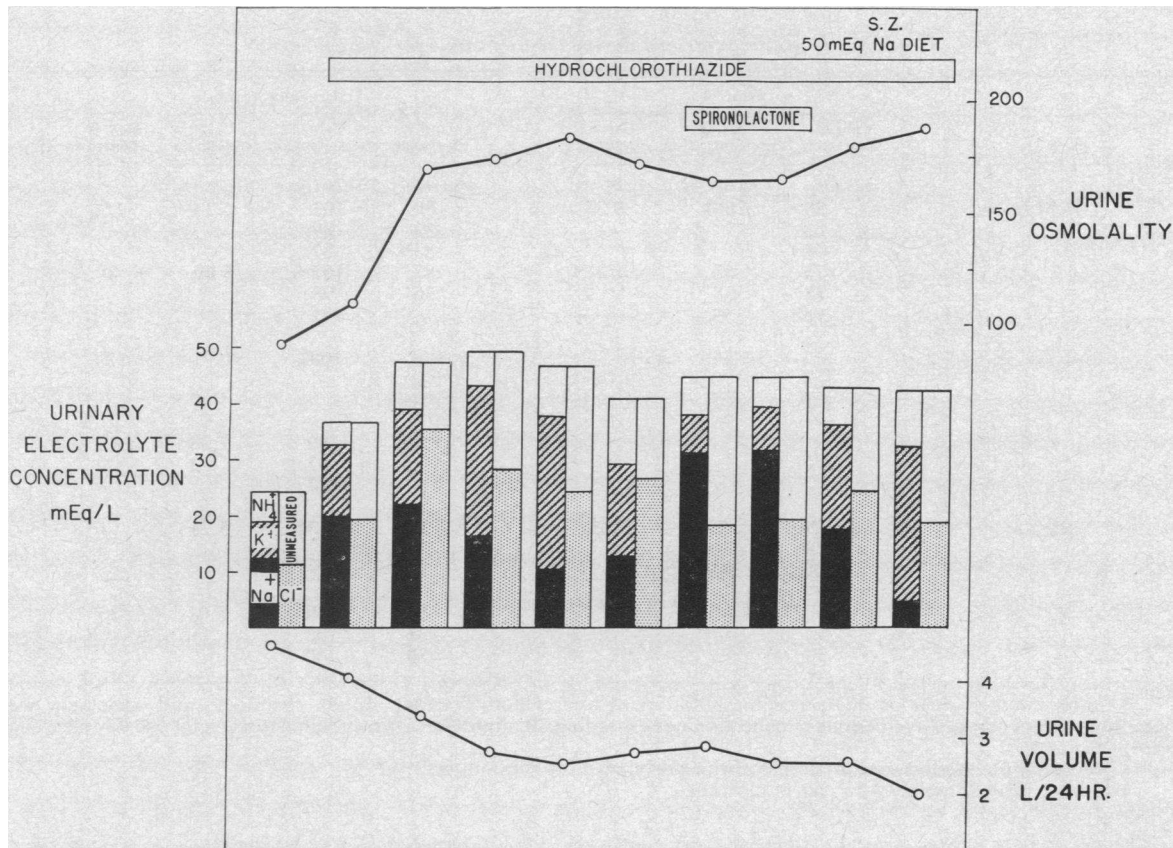


FIG. 4. URINARY COMPOSITION DURING THE ADMINISTRATION OF HYDROCHLOROTHIAZIDE. Days are consecutive days of study. The last day of control observations is shown. Bars indicate the sum of the individual cation and anion concentrations. Spironolactone was given orally as Aldactone, 200 mg every 8 hours for 2 days. Note further diminution in urine volume after increased loss of sodium during administration of spironolactone. Administration of hydrochlorothiazide constant as indicated.

nary volume. In addition, the continued loss of sodium was prevented further by a decreasing urinary sodium concentration associated with an increasing potassium (and to a lesser extent ammonia) concentration, while total electrolyte concentration was essentially unchanged (Figure 4). That this means of conserving sodium (by substitution in the urine of potassium) was mediated by endogenous aldosterone is suggested by the reversal of this relationship during the two days when spironolactone (Aldactone) was administered (Figure 4). The latter agent resulted in diminished concentrations of potassium and ammonia and increased concentrations of sodium in the urine. It is also noteworthy that spironolactone did not alter urinary volume, osmolality, or total electrolyte concentration.

These data are in general agreement with the findings of others (20, 21) and suggest that the adaptive response to the natriuresis induced by hydrochlorothiazide is manifested in at least two ways: 1) an effect of endogenous mineralocorticoid which results in the substitution in the urine of potassium and ammonia for sodium, and 2) a diminution in total electrolyte excretion associated with decreased urine volume, but little change in the total concentration of urinary solutes. As will be discussed subsequently, the latter mechanism may represent decreased delivery of isotonic filtrate to the distal nephron and may account for the antidiuretic effect of these drugs.

Other effects of hydrochlorothiazide. During the period of therapy with hydrochlorothiazide body weight decreased by 0.8 to 1.5 kg. The most

TABLE V
Clearances of inulin before and during therapy with hydrochlorothiazide*

Subject	Control			Hydrochlorothiazide			Day of therapy
	Inulin clearance	Urine concentration	Urine volume	Inulin clearance	Urine concentration	Urine volume	
	<i>ml/min</i>	<i>mOsm/kg</i>	<i>L/24 hrs</i>	<i>ml/min</i>	<i>mOsm/kg</i>	<i>L/24 hrs</i>	
D.M.†	a) 80	68‡	9.35	80	103	4.23	12
	85			83	89		
	78			83	87		
	b) 75	58	8.46	87	107	5.09	6
	88	58		86	98		
	78	59					
R.W.	113	73	13.41	103	108‡	6.91	5
	123	70		102			
	120	67		104			
				118	80	7.38	17
				120	87		
				118	87		
J.W.	97	55	9.51	76	113‡	5.74	4
	90	59		79			
	83	55		75			
				89	109	5.04	15
				82	105		
				88	100		

* Control studies done on day preceding initiation of hydrochlorothiazide. Inulin clearances and osmolality were determined from consecutive periods of collection not exceeding 30 minutes. Urine volume is given for the day clearances were measured.

† Two separate studies with hydrochlorothiazide shown for this subject.

‡ 24-hour urine osmolality on day of clearance.

rapid period of weight loss was during the first days of therapy, when there was an excess excretion of sodium and a progressive diminution in urinary volume. There was a rapid return to control of body weight when the antidiuresis was terminated by cessation of the drug, or by the addition of sodium to the diet. The voluntary daily intake of fluid changed qualitatively with the changes in urinary volume. Plasma osmolality fell during the periods of administration of hydrochlorothiazide by mean values ranging from 3 to 10 mOsm per kg, and there were associated modest depressions in serum sodium concentrations (mean values 133 to 139 mEq per L). These depressions of serum osmolality and serum sodium occurred during the first few days of therapy and remained largely unchanged thereafter. Serum potassium concentrations, however, showed a progressive decline throughout the periods of therapy with hydrochlorothiazide, with values falling as low as 2.6 mEq per L. The low values for serum potassium were returned to normal during the two days that spironolactone was administered to two subjects.

At no time were abnormal serum concentrations of protein, urea nitrogen, or creatinine noted (Table IV). There was never clinical evidence of dehydration, weakness, or other discomfort during the periods of administration of hydrochlorothiazide.

Values for the clearance of inulin in three subjects are given in Table V. Although the clearance of inulin during therapy with hydrochlorothiazide was depressed in two of the measurements in two subjects, this was not a consistent finding in six determinations in the three subjects shown.

Hydrochlorothiazide has been administered to two subjects for a period of six to twelve months. The drug has been given daily as a single 25- or 50-mg dose in conjunction with daily potassium supplements and a diet of restricted sodium chloride content. This has resulted in a significant decrease in urine volumes as judged by less frequent urination and less enuresis. There have been no apparent side effects and serum urea nitrogen and creatinine have remained within normal limits. A continued deficit of potassium has been suggested by serum concentrations of low normal

values (3.0 to 3.5 mEq per L), but frank hypokalemia has been avoided by a daily supplement of 30 to 60 mEq of potassium as potassium chloride.

DISCUSSION

The present report of an inverse relationship between the dietary intake of sodium and the anti-diuretic response to hydrochlorothiazide in patients with diabetes insipidus is in keeping with the findings of Cutler, Kleeman, Dowling, and Maxwell (7) and Havard and Wood (9, 12), who reported that a high intake of sodium either abolished or limited the antidiuresis associated with administration of this drug.

It has been recognized for some time that a direct relationship exists between the dietary intake of sodium and the magnitude of an induced water diuresis (22). Such observations have been extended to demonstrate that increased rates of excretion of many solutes result in augmentation of water diuresis (23). Since during water diuresis (absence of antidiuretic hormone) the distal convolution (24), and probably the collecting duct (25), are virtually impermeable to water, it would appear reasonable that large changes in volume would not occur within the distal nephron, and changes in urine volume during water diuresis must, to a major degree, reflect changes in the amount of filtrate escaping reabsorption in the proximal segment of the nephron. Therefore, since dilute urine is produced by the reabsorption of solute without water (in the absence of antidiuretic hormone) in the distal portions of the nephron (24), the volume of dilute urine excreted would be conditioned by the volume of filtrate delivered to the distal segments.

The mechanisms governing the extent to which the glomerular filtrate is reabsorbed in the proximal nephron are unknown. The influence of dietary sodium on sodium excretion (26) and in turn the influence of sodium excretion on urine volume during water diuresis (as discussed above) suggest, however, that some effect of total body sodium (such as extracellular fluid volume) bears a direct relationship to the volume of filtrate escaping proximal tubular reabsorption.

On the basis of the present observations it is suggested that when thiazide derivatives are administered to patients with diabetes insipidus, the

immediate effect is an increased excretion of electrolyte without an increase in urinary volume, resulting from the action of these agents on solute reabsorption in the distal nephron. As electrolyte losses continue, an additional stimulus (possibly mediated through sodium loss and contraction of the extracellular volume) results in diminished delivery of filtrate to the distal nephron (and, in turn, diminished final urine volume). This could be accomplished either by small decreases in the rate of glomerular filtration, or by an absolute increase in proximal tubular reabsorption. This sequence of events is evident during the first 24 to 48 hours of therapy with hydrochlorothiazide. Such changes appear to take place in the absence of clinically apparent depletion of sodium and may merely be an exaggerated manifestation of a normal mechanism whereby sodium excretion is in part regulated. That these changes are not mediated by aldosterone is suggested by the present observations demonstrating the failure of an aldosterone antagonist to block the antidiuretic effect of hydrochlorothiazide and the failure of DOCA to mimic the antidiuretic effect of the thiazide or mercurial diuretic.

Further evidence suggesting diminished delivery of filtrate to the distal nephron during the antidiuresis of sodium depletion is afforded by the observation of persistent antidiuresis after withdrawal of hydrochlorothiazide and prior to sodium repletion. Such findings may be interpreted as indicating that a sufficiently low flow exists through the distal nephron so that the proportion of water which moves out of the tubular lumen is sufficient to preclude the excretion of urine of minimal osmolality.²

Also consistent with this premise is the manner in which electrolyte balance was achieved during the administration of hydrochlorothiazide. Al-

² Even in the complete absence of antidiuretic hormone or its effect, it is unlikely that the distal nephron is completely impermeable to water, and small net transfers of water may occur along the concentration (water) gradient from tubular lumen into the interstitium (27). With high rates of urine flow during water diuresis this net loss of water is probably insignificant in terms of altering the final urine volume or concentration. As flow through the distal nephron diminishes, however, this loss of water may reach proportions sufficient to increase urine osmolality in the absence of antidiuretic hormone (28).

though sodium conservation was effected to a large measure by replacement in the urine with potassium and ammonia, total electrolyte balance was approached by a reduction in total cation excretion as urine volume decreased, while little change occurred in the total concentration of electrolytes (Figure 4). If this diminution in total electrolyte excretion represented decreased delivery of filtrate to the distal nephron, then the losses of electrolyte induced by hydrochlorothiazide would diminish as less substrate (sodium) reached the distal sites where the agent acts (1-3).

An alternative explanation for the antidiuresis of hydrochlorothiazide administration is that the thiazide derivatives increase the permeability to water of the distal nephron in a fashion similar to antidiuretic hormone. This would appear unlikely for several reasons. The antidiuresis is not dependent upon the continued presence of hydrochlorothiazide, and a qualitatively similar antidiuresis followed losses of sodium from mercaptopurin. In addition, urine osmolalities never reached values as great as that of plasma—a response which should be anticipated with only small amounts of antidiuretic hormone (27). Further, *in vitro* experiments with a vasopressin-sensitive membrane have failed to demonstrate any vasopressin-like quality of chlorothiazide on net water movement along an osmotic gradient (29).

The antidiuretic effect of the mercurial reported herein is in contrast to the report of Crawford, Kennedy, and Hill, who observed no antidiuresis during the duration of a "trial period of twenty-four to forty-eight hours" on mersalyl (13). Since mercurial diuretics appear to interfere with the isotonic reabsorption of sodium (30-32), however, these agents would produce an increased final urine volume, and an antidiuretic effect would only be expected during the period following the mercurial diuresis and prior to a repletion of the losses of sodium.

It has been suggested that the thiazide derivatives are in some way antagonistic to the renal action of mineralocorticoids (33). The finding in the present studies of a clear effect of spironolactone, despite the presence of hydrochlorothiazide, suggests a distinct renal action of endogenous mineralocorticoid in the presence of a thiazide

derivative. Also, Kahn has recently observed the expected effect of chlorothiazide on electrolyte excretion in adrenalectomized animals (34).

Although the reduction in urinary volume is analogous to that which would be expected from dietary restriction of sodium, the combination of hydrochlorothiazide with a limited intake of sodium offers a means of reducing body sodium and urinary volume to an even greater extent than by diet alone, and as previously suggested (13), these agents may have an important place in the management of patients with vasopressin-resistant diabetes insipidus. Since the depletion of body sodium should be self-limited owing to the diminished delivery of filtrate to the sites where these agents are active, the primary hazard would appear to be excessive urinary losses of potassium and hypokalemia.

SUMMARY

The antidiuretic properties of hydrochlorothiazide were studied in four subjects with congenital vasopressin-resistant diabetes insipidus. Evidence is presented which suggests that the antidiuresis results from mild sodium depletion and is not due to a unique property of the thiazide derivatives. A mechanism is discussed whereby reduction in body sodium may lead to intrarenal alterations resulting in a reduced volume of urine of higher osmolality. Data are presented which suggest that the natriuretic effect of hydrochlorothiazide may be overcome by the endogenous release of aldosterone and by diminishing the delivery of filtrate to the distal sites where this agent is active.

It is concluded that when employed in conjunction with supplemental potassium and a restricted dietary intake of sodium, hydrochlorothiazide is of value in reducing the urine output of patients with vasopressin-resistant diabetes insipidus.

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