THE PREVENTION OF ACTH-INDUCED SODIUM RETENTION BY THE USE OF POTASSIUM SALTS: A QUANTITATIVE STUDY

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Administration of large doses of either corticotropin (ACTH) (1) or the adrenal steroids (2–5) to human subjects ordinarily results in an initial phase of sodium retention which is often accompanied by increased excretion of potassium in the urine and by a decrease in intracellular potassium (6). In order to minimize potassium depletion, it has become common practice to add supplements of potassium salts to the diets of patients receiving large doses of ACTH or cortisone. The use of such supplements was also found to be extremely effective in overcoming the sodium retention induced by ACTH and by cortisone (7). The present study was designed to clarify the mechanism of the sodium diuresis which follows the ingestion of large amounts of potassium salts.

SUBJECTS AND METHODS

Thirty experiments were carried out in 14 subjects. Seven subjects were men, seven woman. Seven subjects had rheumatoid arthritis, one disseminated lupus erythematosus, one dermatomyositis, one gout, one multiple sclerosis, one hyperinsulinism, one Cushing's syndrome, and one no demonstrable disease. No subject with evidence of disease of the liver, kidneys, or of the pituitary or adrenal glands was included in this series.

Throughout the course of the study each subject was maintained on a constant diet. Total urinary output was collected. When appropriate, specimens of feces, saliva, and blood were taken for electrolyte determination. In most experiments, potassium salts were administered orally in small divided doses; in a few cases, the potassium salt was given by continuous intravenous infusion. ACTH was administered intramuscularly, either in aqueous solution every six hours or in 16 per cent gelatin every 24 hours. When either cortisone acetate or hydrocortisone was used, the daily dose was divided into four equal parts administered orally every six hours.

The following laboratory methods were employed: Sodium and potassium determinations were made, using a flame photometer (Perkin-Elmer Model 52-A) with lithium as an internal standard. Chloride was determined by the method of Schales and Asper (8, 9). Inorganic phosphorus was determined by the method of Fiske and Subbarow (10). Urinary ammonia was determined by the method of Folin and Bell (11). Urinary pH was estimated on freshly voided specimens by means of nitrazine paper. Urinary titratable acidity[2] was determined by an adaptation of the method of Henderson and Palmer (12). In preparation for carbon dioxide-plus-bicarbonate determinations, urine was collected under oil in small amounts of carbon dioxide-poor sodium hydroxide solution; carbon dioxide-plus-bicarbonate was then determined on a Van Slyke and Neill manometric blood gas apparatus. Urine specimens for all other chemical determinations were collected in chemically clean glassware containing a known excess of sulfuric acid.

RESULTS

Representative results obtained in each category of experiments are as follows:

The regularity with which administration of ACTH results in retention of sodium in human subjects is illustrated in Figure 1. Subject A. A. received five courses of treatment, each employing a different preparation of ACTH. Retention of sodium occurred during administration of each preparation. Sodium excretion tended to return to control levels after the initial three or four days of treatment, but a frankly negative sodium balance was never observed as long as effective dosage of ACTH was maintained. The abrupt withdrawal of each preparation was followed by a marked diuresis of sodium. In our experience this pattern of sodium retention occurs invariably

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[2] The term "titratable acidity" as employed in this report actually refers to "titratable acidity minus carbon dioxide," inasmuch as carbon dioxide was driven off by "boiling" the urine under reduced pressure before titrating to a pH of 7.4.

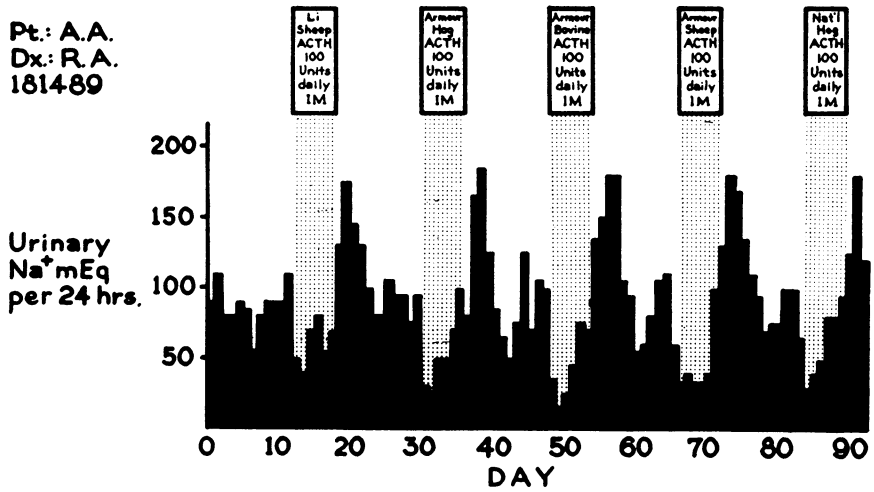

FIG. 1. URINARY SODIUM AS INFLUENCED BY ADMINISTRATION AND WITHDRAWAL OF FIVE DIFFERENT PREPARATIONS OF ACTH IN SUBJECT A. A. WHILE RECEIVING A CONSTANT DIET

in subjects with normal adrenals during continuous treatment with ACTH. The pattern may be profoundly modified, however, when potassium therapy is superimposed upon ACTH therapy.

Typically, the administration of potassium acetate results in sodium diuresis for approximately two days. Sodium excretion then returns to control levels, and there may even be a phase of sodium retention despite continued administration of the potassium salt. The sodium retention produced by ACTH can be completely prevented by simultaneous administration of large doses of potassium acetate (Figure 2). Subject L. G., after a control period of six days, was given potassium acetate, 360 mEq. daily, for a period of 12 days. This particular experiment was atypical in that only a minimal sodium diuresis occurred during the first two days of potassium administration. When ACTH was started on the seventh day of potassium administration, there was no evidence whatever of sodium retention. That potassium acetate had actually prevented the sodium-retaining effect of ACTH became apparent on the nineteenth day of the study, when the potassium salt was withdrawn. At this time the unopposed influence of ACTH became manifest, and the subject entered a phase of marked sodium retention. Finally, on the twenty-fifth day of the study, ACTH was withdrawn and a marked diuresis of sodium ensued.

The complete reversal of ACTH-induced sodium retention by the administration of potassium acetate is illustrated in Figure 3. Subject R. D., after an initial control period, was treated with 25 international units of ACTH, injected intramuscularly every six hours, and the expected phase of sodium retention was readily apparent. On the seventh day of ACTH therapy, the administration of potassium acetate was begun, and despite the fact that ACTH was continued, a striking sodium diuresis occurred, which resulted in a loss of more sodium than had been retained previously. It will be noted that the natriuretic effect of potassium acetate was maximal for only two days and disappeared after four days. After ACTH was withdrawn on the nineteenth day of the study, the sodium loss which usually follows sudden withdrawal of this hormone was hardly preceptible. Finally, on the twenty-fifth day of the study, potassium acetate was withdrawn, and a phase of almost complete sodium retention ensued. A reactive rebound phenomenon is well illustrated in this study: First, the sodium loss which occurred when potassium was administered was greater in magnitude than the preceding ACTH-induced sodium retention; second, the sodium retention which followed withdrawal of potassium exceeded in magnitude the sodium loss which occurred when potassium was administered.

Data presented in Figure 4 show that potassium acetate will also induce sodium diuresis in subjects not receiving ACTH. Subject A. A., who had

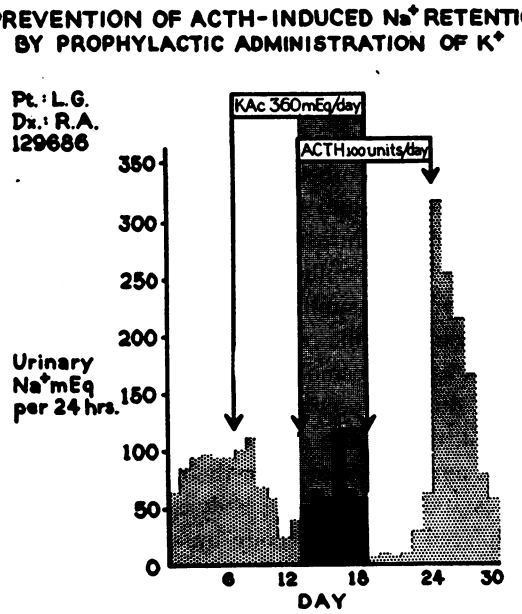

FIG. 2. URINARY SODIUM AS INFLUENCED BY POTASSIUM ACETATE AND ACTH, ADMINISTERED SEPARATELY AND SIMULTANEOUSLY TO SUBJECT L. G. WHILE RECEIVING A CONSTANT DIET

not been treated previously with ACTH, showed a moderate loss of sodium when he received 360 mEq. of potassium acetate in one day. On the following days, sodium was retained. Subsequently, this subject was given the same amount of potassium acetate plus 100 units of ACTH for one day, and a similar sodium diuresis occurred. This indicates that the natriuretic effect of potassium acetate is not limited to subjects receiving corticotherapy.

It will be noted, however, that the sodium diuresis in subject A. A. was much less in magnitude than that observed in other subjects given potassium acetate in comparable doses, most likely because this subject, not having received ACTH, had not retained an excess of sodium before the potassium was administered. As shown in Figure 5, it appears that the degree of sodium loss which occurs when potassium acetate is given is proportional to the body stores of sodium. For 17 days, subject N. C. was given a diet in which sodium intake was severely restricted (6 mEq. per day). During the first six days, urinary excretion of sodium gradually came into equilibrium with sodium intake. Administration of ACTH from the seventh day on resulted in little or no sodium retention. When potassium acetate (360 mEq. per day) was added to the ACTH regimen from the eleventh through the fourteenth days, there was a slight but definite loss of sodium. Withdrawal of potassium was followed by a return to sodium equilibrium. Thus, administration of potassium acetate induces a negative sodium balance, even when not preceded by a phase of sodium retention; the sodium diuresis, however, is less intense when there has not been a preceding phase of sodium retention.

A number of theoretically possible mechanisms were tested in an effort to explain the natriuretic action of potassium salts. Is the natriuretic action a function of the potassium ion alone, or is it influenced by the type of anion administered with the potassium? The fact that potassium salts other than potassium acetate are also effective in producing sodium diuresis is illustrated by the experiments outlined in Tables I, II, and III. Subject V. N. (Table I) had been given intramuscular injections of highly purified ACTH gel, 40 international units daily, for a month by the time this study was begun and had presumably already passed through the early sodium-retaining phase. When

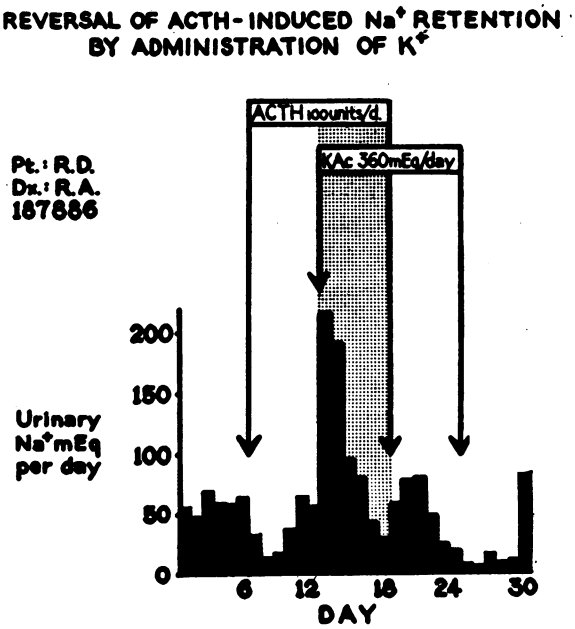

FIG. 3. URINARY SODIUM AS INFLUENCED BY ACTH AND POTASSIUM ACETATE ADMINISTERED SEPARATELY AND SIMULTANEOUSLY TO SUBJECT R. D. WHILE ON A CONSTANT DIET

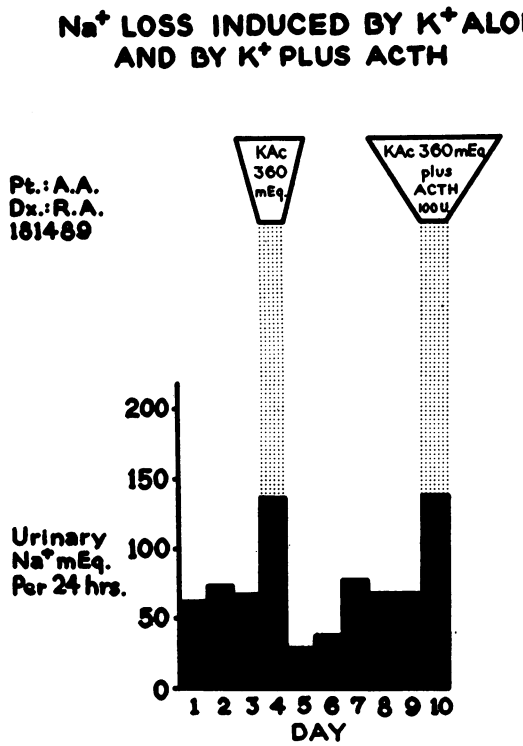

FIG. 4. URINARY SODIUM AS INFLUENCED BY POTASSIUM ACETATE ADMINISTERED ALONE AND IN CONJUNCTION WITH ACTH WITHOUT A PRECEDING PHASE OF ACTH-INDUCED SODIUM RETENTION (SUBJECT A. A.)

potassium chloride, 360 mEq. per day, was administered for six days, a very large loss of sodium occurred. Withdrawal of potassium chloride again permitted sodium retention.

As shown in Table II, the natriuretic effect of neutral potassium phosphate (pH 7.0) may not be obvious when the salt is administered orally, perhaps because phosphate given orally in such large doses causes diarrhea. But natriuresis is readily apparent when the potassium phosphate is given parenterally. In subject N. C., the continuous intravenous infusion of 360 mEq. of potassium in this form for a period of 15 hours resulted in a definite increase in urinary sodium. Similarly, as shown in Table V, the intravenous administration of 180 mEq. of potassium phosphate (pH 7.5) to a patient with hypokalemia due to Cushing's syndrome resulted in a striking sodium diuresis even though the serum potassium never reached normal levels.

Inasmuch as potassium acetate, potassium chloride, and potassium phosphate are all natriuretic agents, it appears that an excess of the potassium ion *per se* may specifically induce sodium excretion.

Is the sodium loss based upon an "osmotic diuresis"? Subject R. Do. (Table III), while receiving no corticotherapy, was given 720 milliosmols of potassium chloride in one day, and a definite sodium diuresis occurred. One week later he was given 720 milli-osmols of potassium acetate in one day, and a similar sodium diuresis occurred. Subsequently, while on the same regimen, he was given 1440 milli-osmols of urea in one day, and no sodium diuresis occurred. It is apparent, therefore, that the sodium diuretic efficacy of potassium salts is not dependent upon their osmotic activity.

Does sodium leave the body simply because it is displaced within the body by an alternative cation, potassium? Figure 6 presents a comparison of sodium and potassium balances during a typical experiment. During the initial control period, the subject (R. D.) was in approximate sodium and potassium equilibrium. Administration of ACTH resulted in a decrease in urinary excretion of so-

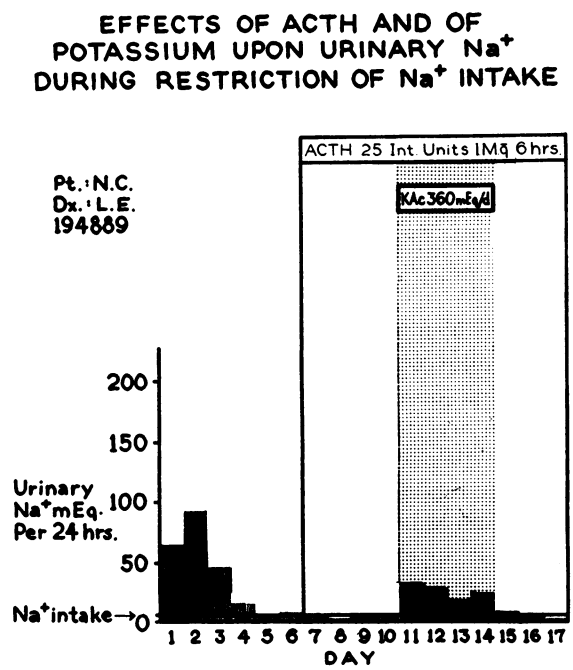

FIG. 5. URINARY SODIUM AS INFLUENCED BY ACTH AND POTASSIUM ACETATE IN SUBJECT N. C. WHILE ON A DIET CONTAINING 6 MEQ. OF SODIUM IN AN ATTEMPT TO PRECLUDE SODIUM RETENTION DURING ACTH ADMINISTRATION

TABLE I

The effects of potassium chloride on urinary electrolytes

Pt. V. N., No. 199815. White, female, 36 years. Dermatomyositis

Day	Treatment		24-Hour urinary						Serum				Salivary	
			Na (*mEq.*)	K (*mEq.*)	Cl (*mEq.*)	P (*mM*)	Titr. ac. (*mEq.*)	NH_3 (*mM*)	Na *mEq./L.*	K *mEq./L.*	CO_2 *mEq./L.*	Cl *mEq./L.*	Na *mEq./L.*	K *mEq./L.*
1–30	ACTH daily													
31	ACTH-gel 40 Int. Units i.m. daily		74	115	95	30	27	83						
32	ACTH-gel 40 Int. Units i.m. daily		66	110	86	29	22	92						
33	ACTH-gel 40 Int. Units i.m. daily		76	108	90	30	26	82						
34	ACTH-gel 40 Int. Units i.m. daily		75	102	95	31	33	83						
35	ACTH-gel 40 Int. Units i.m. daily		73	123	95	27	24	96						
36	ACTH-gel 40 Int. Units i.m. daily		82	108	107	30	0	80	138	2.7	36	95	7	29
37	ACTH-gel 40 Int. Units i.m. daily	KCl, 27 Gm. orally, daily	228	306	296	18	−128	13						
38	ACTH-gel 40 Int. Units i.m. daily	KCl, 27 Gm. orally, daily	220	436	481	24	−33	25					7	30
39	ACTH-gel 40 Int. Units i.m. daily	KCl, 27 Gm. orally, daily	126	461	407	25	11	30	140	4.4	28	106		
40	ACTH-gel 40 Int. Units i.m. daily	KCl, 27 Gm. orally, daily	66	457	418	27	31	34						
41	ACTH-gel 40 Int. Units i.m. daily	KCl, 27 Gm. orally, daily	152	432	482	25	26	25						
42	ACTH-gel 40 Int. Units i.m. daily	KCl, 27 Gm. orally, daily	120	444	455	25	20	21	142	4.8	27	101	6	29
43	ACTH-gel 40 Int. Units i.m. daily		42	187	181	31	50	32						
44	ACTH-gel 40 Int. Units i.m. daily		21	75	49	24	40	58	139	3.4	31	94	5	28
45	ACTH-gel 40 Int. Units i.m. daily		42	98	105	25	35	81						
46	ACTH-gel 40 Int. Units i.m. daily		72	99	105	24	26	84	143	3.1	30	94		
47	ACTH-gel 40 Int. Units i.m. daily		82	109	100	26	25	96						
48	ACTH-gel 40 Int. Units i.m. daily		74	98	95	28	20	80	140	3.1	35	96	6	32

dium and a positive sodium balance, whereas the over-all potassium balance did not change. When large amounts of potassium acetate were administered, there was an initial phase of potassium retention concurrent with a striking loss of sodium. However, during this initial phase the absolute magnitude of the sodium loss was much greater than the magnitude of the potassium retention. Thus, the sodium loss could only be partially explained in terms of its displacement by potassium. It will be noted also that following the withdrawal of potassium acetate, the sodium retention was far greater in magnitude than the simultaneous potassium loss. This indicates that the administration or withdrawal of potassium influences the excretion of sodium to an extent which exceeds the direct exchange of one cation for the other.

Does potassium cause an increase in sodium excretion by inhibiting the cation exchange mechanism for acidification of urine? Subject L. G. (Table IV), who received ACTH in constant doses throughout the course of this study, was treated for six days with potassium acetate, 360 mEq. per day. During this six-day period the excretion of titratable acid ceased entirely, and the excretion of ammonia was sharply reduced. Presumably, complete inhibition of cation exchange in the renal tubules would result in a disappearance of titratable acid and ammonia from the urine and an equivalent increase in urinary sodium (13). But,

TABLE II

The effect of neutral potassium phosphate on urinary electrolytes

Pt. N. C., No. 194889. White, female, 33 years. Disseminated lupus erythematosus

Day	Treatment		24-Hour urinary Na (*mEq.*)	K (*mEq.*)	Cl (*mEq.*)	P (*mM*)	Titr. ac. (*mEq.*)	NH_3 (*mM*)
1–6	Hydrocortisone 20 mg. orally every 6 hours							
7	Hydrocortisone 20 mg. orally every 6 hours		80	55	82	21	21	47
8	Hydrocortisone 20 mg. orally every 6 hours		79	58	83	22	19	46
9	Hydrocortisone 20 mg. orally every 6 hours		82	51	88	21	23	48
10	Hydrocortisone 20 mg. orally every 6 hours		77	52	81	25	17	45
11	Hydrocortisone 20 mg. orally every 6 hours	KH_2PO_4 12.2 Gm. K_2HP_4 23.5 Gm. (orally)	125	217	131	65	34	29
12	Hydrocortisone 20 mg. orally every 6 hours		89	80	60	45	31	37
13	Hydrocortisone 20 mg. orally every 6 hours		73	65	73	37	25	38
14	Hydrocortisone 20 mg. orally every 6 hours		61	72	54	33	36	53
15	Hydrocortisone 20 mg. orally every 6 hours		58	68	55	27	27	56
16	Hydrocortisone 20 mg. orally every 6 hours		53	62	47	24	18	47
17	Hydrocortisone 20 mg. orally every 6 hours	KH_2PO_4 12.2 Gm. K_2HP_4 23.5 Gm. (intravenously)	176	306	180	236	62	44
18	Hydrocortisone 20 mg. orally every 6 hours		57	109	72	47	38	45
19	Hydrocortisone 20 mg. orally every 6 hours		40	80	62	42	33	47

it will be noted that in this patient the absolute magnitude of the cation exchange performed by the kidneys during pre-potassium periods was not more than 65 mEq. per day (20 mEq. as titratable acidity plus 45 mEq. as ammonia). On the first day of potassium administration, the negative sodium balance was approximately 160 mEq. per day. Therefore, even complete inhibition of the renal tubular cation exchange mechanism for acidification of the urine cannot account for the magnitude of the natriuretic effect of potassium if it is assumed that titratable acid-ammonia excretion is a valid measure of tubular $H^+ - Na^+$ exchange.

Over-all changes in the excretion of electrolytes during administration of large amounts of potassium salts were studied in six subjects. Table I, II, and IV summarize data obtained in representative studies of three subjects. These subjects had been receiving ACTH or hydrocortisone, and, by the time the study was initiated, had already passed through the initial phase of sodium retention and were in approximate sodium equilibrium. Potassium chloride was given to one subject, potassium phosphate to the second, and potassium acetate to the third. All three subjects lost sodium initially when potassium was given, and all retained sodium after potassium was withdrawn. In all studies the pH of the urine increased during administration of potassium; this effect was most marked with potassium acetate and least marked with potassium phosphate. When potassium chloride or potassium acetate was given, urinary ammonia and titratable acidity became negligible, urinary phosphorus decreased sharply, and urinary carbon dioxide-plus-bicarbonate increased markedly. With potassium phosphate, however, urinary titratable acidity-plus-ammonia actually increased.

Interestingly, in most of these experiments loss of sodium was greater than loss of chloride when either potassium acetate or potassium chloride was used. For instance, in subject L. G. administration of potassium acetate resulted in loss of both

TABLE III

Comparison of the effects of urea and potassium salts on urinary electrolytes
Pt. R. Do., No. 130120. White, male, 31 years. Gout

Day	Treatment	24-Hour urinary Na (*mEq.*)	K (*mEq.*)	Cl (*mEq.*)	P (*mM*)	Titr. ac. (*mEq.*)	NH_3 (*mM*)	N (*Gm.*)
1–3	Equilibration period							
4	Control period	99	85		26			
5	Control period	98	80	107	24			
6	Control period	118	73	120	23			
7	Control period	110	82	122	23			
8	Control period	111	81	124	23	17	27	
9	KCl, 27 Gm. orally	176	273	358	20	11	16	
10	Control period	127	196	282	23	25	22	
11	Control period	117	117	151	33	33	26	
12	Control period	114	96	128	30	29	25	
13	Control period	117	97	131	27			
14	Control period	116	86	129	27	24	22	
15	Control period	120	77	125	26	25	22	
16	K Acetate, 36 Gm. orally	199	288	227	16	−108	8	
17	Control period	89	150	74	26	−34	7	
18	Control period	108	111	93	32	3	11	15
19	Control period	110	88	124	26			16
20	Control period	109	101	119	31			15
21	Control period	105	101	125	29			17
22	Control period	98	107	114	29			17
23	Urea, 85 Gm. orally	117	96	138	28			48
24	Control period	96	87	111	27			23
25	Control period	113	83	120	27			20

sodium and chloride, but the magnitude of the sodium loss was much greater than that of the chloride loss. When subject V. N. was given potassium chloride, there was a net retention of both potassium and chloride, associated with a marked loss of sodium. Potassium phosphate, however, administered intravenously to subject N. C., resulted in loss of both sodium and chloride in approximately equal quantities.

Although the administration of potassium chloride tends to correct the hypokaliemic alkalosis of Cushing's syndrome (see Table I), the natriuretic action of potassium is not dependent upon the presence of either alkalosis or hypokaliemia. Of the present series of subjects, all of whom showed natriuretic responses to potassium, only two had hypokaliemic alkalosis (V. N. and C. K.).

The urine is only one of many body fluids whose electrolyte composition is affected by adrenal steroids. The sodium-potassium ratio of saliva, for example, may be greatly decreased during treatment with ACTH or cortisone (14). Data presented in Table I show that in subject V. N., the very low salivary sodium-potassium ratio induced by ACTH was not modified by doses of potassium chloride which considerably altered the urinary electrolyte pattern. It would appear, therefore, that potassium does not overcome the effect of ACTH upon the salivary sodium-potassium ratio at a time when it does modify the effect of ACTH upon the urinary electrolyte pattern.

DISCUSSION

Potassium salts tend to reverse many of the effects of adrenal steroids upon electrolyte metabolism. It is conceivable that part of the sodium loss which follows administration of potassium salts is a result of a readjustment of the intracellular electrolyte pattern, *i.e.*, increase in intracellular potassium and decrease in intracellular sodium. This readjustment would be most apt to occur in subjects in whom there had been a prior depletion of intracellular potassium, which could be induced by any

TABLE IV

Effect of potassium acetate on urinary electrolytes

Pt. L. G., No. 129686. White, female, 33 years. Rheumatoid arthritis

Day	Treatment		24-Hour urinary					
			Na (*mEq.*)	K (*mEq.*)	Cl (*mEq.*)	P (*mM*)	Titr. ac. (*mEq.*)	NH_3 (*mM*)
1	ACTH-gel 40 Int. Units i.m. daily		54	98	64	22	21	45
2	ACTH-gel 40 Int. Units i.m. daily		70	92	86	22	13	40
3	ACTH-gel 40 Int. Units i.m. daily		48	83	60	22	17	47
4	ACTH-gel 40 Int. Units i.m. daily		63	83	70	22	16	48
5	ACTH-gel 40 Int. Units i.m. daily	KAc, 36 Gm. orally, daily	220	353	122	11	−307	10
6	ACTH-gel 40 Int. Units i.m. daily	KAc, 36 Gm. orally, daily	140	402	115	14	−269	10
7	ACTH-gel 40 Int. Units i.m. daily	KAc, 36 Gm. orally, daily	130	492	131	17	−236	11
8	ACTH-gel 40 Int. Units i.m. daily	KAc, 36 Gm. orally, daily	118	405	108	16	−288	12
9	ACTH-gel 40 Int. Units i.m. daily	KAc, 36 Gm. orally, daily	136	446	84	21	−323	13
10	ACTH-gel 40 Int. Units i.m. daily	KAc, 36 Gm. orally, daily	146	415	111	25	−296	8
11	ACTH-gel 40 Int. Units i.m. daily		22	123	36	31	23	22
12	ACTH-gel 40 Int. Units i.m. daily		30	93	51	24	12	25
13	ACTH-gel 40 Int. Units i.m. daily		35	110	62	29	11	34
14	ACTH-gel 40 Int. Units i.m. daily		26	73	37	29	7	35

of a number of factors, including corticotherapy. On the other hand, part of the sodium loss which occurs when potassium acetate or potassium chloride is administered appears to result from a direct action of potassium upon the renal tubules. Berliner, Kennedy, and Orloff (15) have postulated that such an action is in the nature of inhibition of the tubular mechanism by which H^+ ions are excreted in exchange for Na^+ ions. If it is assumed that titratable acid-ammonia excretion is a valid measure of tubular $H^+ - Na^+$ exchange, then two lines of evidence indicate that this mechanism cannot account for the entire sodium loss which follows administration of potassium. First, excretion of titratable acid and ammonia may be regarded as one means of conserving an equivalent amount of sodium. Theoretically, complete suppression of the mechanism for excreting titratable acid and ammonia should result in an equivalent increase in sodium excretion. Several of the balance studies showed, however, that the total amount of titratable acid-plus-ammonia excreted during control periods is much less than the sodium loss observed during administration of potassium. Therefore, even complete suppression of titratable acid-ammonia excretion could not account for all of the actual sodium loss. Second, excretion of titratable acid-plus-ammonia became increased when potassium phosphate was administered. Here, there was no reason to believe that the sodium conservation mechanism under question was suppressed. Nevertheless, the fact that a marked sodium loss did occur suggests that there is more involved in potassium-induced natriuresis than suppression of fixed-base conservation mechanisms. In short, to the extent that potassium *does* inhibit $H^+ - Na^+$ exchange in the renal tubules one may expect a resultant natriuresis; however, potassium *also* induces natriuresis under conditions in which $H^+ - Na^+$ exchange might be occurring at a normal or even increased rate.

On the other hand, it could be assumed that the quantity of H^+ ion appearing in the urine either as titratable acid or with ammonia does not actually represent the total amount of tubular $H^+ - Na^+$ exchange but only a minor fraction thereof. This

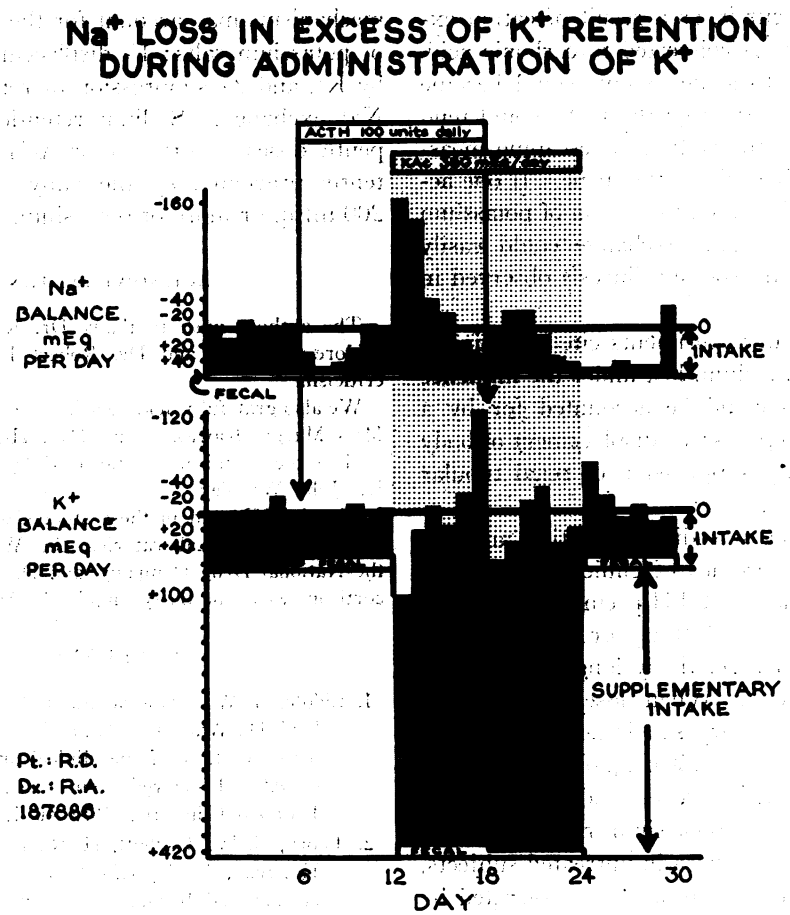

FIG. 6. SODIUM BALANCE AND POTASSIUM BALANCE IN SUBJECT R. D. DURING TREATMENT WITH ACTH AND POTASSIUM ACETATE

Note that the negative sodium balance (black area) is substantially greater than the positive potassium balance (white area) during the first two days of potassium administration.

TABLE V

Effect of potassium phosphate (pH 7.5) on urinary and serum electrolytes

Pt. C. K., No. 81625. White, female, 30 years. Cushing's syndrome

		24-Hour urinary						Serum			
Day	Treatment	Na (*mEq.*)	K (*mEq.*)	Cl (*mEq.*)	P (*mM*)	Titr. ac. (*mEq.*)	NH_3 (*mM*)	Na *mEq./L.*	K *mEq./L.*	Cl *mEq./L.*	CO_2 *mEq./L.*
1	None	64	97	75	32	15	65	140	2.8	92	35
2	None	81	94	103	33	8	60				
3	None	55	93	69	24	12	45	141	2.7	95	36
								Time			
4	KH_2PO_4 2.0 Gm. K_2HPO_4 15.0 Gm. (Intravenously from 0 to 16 hrs.)	297	194	240	67	25	41	0 hr. 143 4 hr. 132 12 hr. 136 24 hr. 134	2.6 3.3 3.6 3.1	94 91 92 94	36 35 32 30
5	None	<1	92	49	27	15	44				
6	None	<1	91	82	21	12	38	138	3.7	92	35

disparity might occur if, as a result of cation exchange, bicarbonate is converted to carbonic acid. The carbonic acid to some extent would become converted to H_2O and CO_2; the CO_2 would tend to diffuse back into the body, thus escaping measurement as titratable acid in the urine. If one accepts this assumption, then the action of potassium in suppressing $H^+ - Na^+$ exchange could easily account for the entire sodium diuresis observed in these studies.

In any case, in all experiments cited in this report the amount of sodium lost under the influence of potassium salts could be accounted for by a summation of two effects: 1) displacement of body Na^+ by K^+, plus 2) suppression of renal tubular $H^+ - Na^+$ exchange.

The complication of sodium retention and potassium depletion becomes of clinical significance only when cortisone or ACTH is employed in relatively large doses (*e.g.*, 100 mg. or more of cortisone daily) and for a relatively long period (*e.g.*, more than one week). When doses greater than this are given and dietary salt is not restricted, a potassium supplement of 200 mEq. or more per day is ordinarily sufficient to prevent sodium retention. Although such doses of potassium frequently cause abdominal cramps or nausea in untreated subjects, even larger amounts are usually well tolerated by subjects receiving corticotherapy. In practice it is best to divide the supplement of potassium into several small doses to be taken throughout the day.

SUMMARY

The oral administration of large doses of either potassium chloride or potassium acetate to human subjects consistently results in a diuresis of sodium. The degree of sodium diuresis is greater in subjects in whom sodium retention has been induced by ACTH or cortisone than in untreated subjects. The administration of potassium chloride and potassium acetate results in a decrease of urinary phosphate, ammonia, and titratable acid and an increase in urinary bicarbonate and chloride. The increase in urinary sodium is proportionately much greater than the increase in urinary chloride. Neutral potassium phosphate, administered intravenously, causes sodium and chloride diuresis, without causing a decrease in urinary titratable acidity-plus-ammonia. It is suggested that two possible mechanisms may account for the natriuretic effect of potassium salts: 1) displacement of body Na^+ by K^+, and 2) suppression of renal tubular $H^+ - Na^+$ exchange. Sodium retention due to therapeutic doses of cortisone or ACTH can be consistently prevented by the daily administration of 200 mEq. or more of potassium.

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