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Research Article

RESPONSE OF NORMAL SUBJECTS TO LARGE AMOUNTS OF ALDOSTERONE [1]

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A major effect of exogenous aldosterone in man is sodium and chloride retention and potassium excretion (1–6). Sodium retention in cases of cardiac failure, cirrhosis and nephrosis, and during sodium or fluid depletion has been associated with increased urinary excretion of this hormone (7–10). Decreased aldosterone excretion has been found with increased urinary sodium excretion during extracellular fluid volume expansion and conversely, increased aldosterone excretion has been found with decreased urinary sodium excretion in extracellular fluid volume depletion (11–13). These findings, which have established the importance of aldosterone in fluid and electrolyte metabolism, appear to conflict with the absence of marked sodium retention and edema in cases of primary aldosteronism (14, 15). It has been suggested that other adrenal steroids may modify the metabolic abnormalities of this syndrome or that an "escape" from sodium retention may occur (16–18).

The present study provides data on the effect of large amounts of aldosterone in normal subjects and indicates that following initial sodium retention, sodium excretion returns approximately to control levels despite continued aldosterone administration.

METHODS AND PROCEDURE

Studies were carried out during the autumn months on two healthy males, aged 28 and 30, who continued their usual activities but avoided vigorous exercise. Subject W. M. received *d,l*-aldosterone 21-monoacetate [4] in sesame oil, 3 mg. intramuscularly daily for 14 days, and Subject T. A. received 3 mg. daily for 4 days and 6 mg. daily for 22 days. The drug was given every eight hours. Constant diets were maintained throughout the study. These provided 3,156 calories, 128 mEq. sodium, 116 mEq. potassium and 21.3 Gm. nitrogen for Subject W. M., and 2,314 calories, 75 mEq. sodium, 84 mEq. potassium and 13.5 Gm. nitrogen for Subject T. A. Oral fluids varied between 1,750 and 2,000 ml. daily. Saliva was collected at 7 a.m. daily (19). Excretion was determined by the analysis of 24 hour urine specimens collected and stored at 5° C. and from stools pooled in three to five day periods. Control periods of six and seven days were initiated two days after the diets began. In this text electrolyte excretion during the periods of and after aldosterone administration will be compared with the average daily electrolyte excretion during these control periods. Measurements were made of sodium and potassium in serum, urine, diet, feces and saliva by flame photometry, creatinine in plasma (20) and urine (21), total nitrogen in urine, feces and diet by a micro-Kjeldahl method, urinary 17-ketosteroids (22) and 17-hydroxycorticosteroids (23), urinary osmolarity cryoscopically using a Fiske osmometer, urinary true glucose (24), arterial pH by glass electrode and urinary aldosterone (25).

RESULTS

General effects

Both subjects responded in a similar manner. Administration of aldosterone produced an initial weight increase which was more rapid in W. M. who consumed more salt (Figures 1 and 2). Weight gain slackened and ceased after an increase in body weight of 2 to 3 Kg. Subject T. A. lost an average of 0.1 Kg. per day during the control period, presumably as a result of slight caloric deficiency in the constant diet. Correcting his daily weight change by this amount indicates a pattern of weight change similar to that of Subject W. M. Arterial diastolic blood pressures increased 10 to 20 mm. mercury with maximal weight gain and remained elevated until aldosterone administration was discontinued. The only objective evidence of edema was slight periorbital

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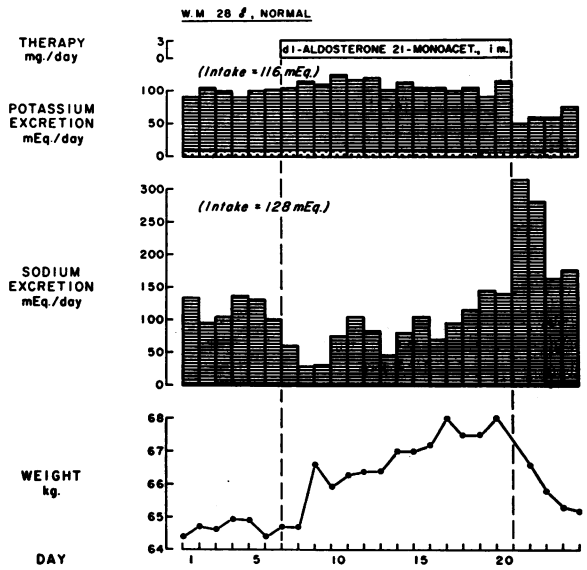

FIG. 1. THE EFFECT OF ALDOSTERONE ON WEIGHT AND SODIUM AND POTASSIUM EXCRETION IN NORMAL SUBJECT W. M. RECEIVING A CONSTANT DIET

Stool electrolyte excretion is indicated by the stippled areas and urinary electrolyte excretion by the cross-hatched areas. Where stippled areas are not seen, the stool electrolyte excretion was less than 1 mEq./day. An escape from sodium retention occurred on the fifth day of aldosterone administration.

puffiness. Headache and malaise occurred during the period of maximal sodium retention but were less severe during episodes of increased urinary volume and sodium excretion. Urinary true glucose excretion and arterial pH were unaffected.

Effect on fluid and electrolytes

Administration of aldosterone resulted in a prompt retention of sodium and an increase in potassium excretion (Tables I and II). There was no apparent relationship between sodium retention and potassium excretion: Sodium retention was greater with higher sodium intake and diminished as the treatment continued; potassium excretion was essentially similar in both subjects and always exceeded the average daily control potassium excretion except for one day in Subject W. M. Consequently, sodium retention initially greatly exceeded potassium excretion, but as treatment continued, the opposite occurred and potassium excretion exceeded sodium retention. Sodium excretion was never less than 10 mEq. per 24 hours despite the large amount of aldosterone, and was smaller in Subject T. A. who received more aldosterone and less sodium than Subject W. M.

Despite continued aldosterone administration, sodium excretion suddenly increased in both subjects. In Subject W. M. this occurred on the fifth day of aldosterone administration, following cumulative weight gain of 1.5 Kg., and cumulative sodium retention of 270 mEq., as compared to the average daily sodium excretion during the control period. In T. A. this occurred on the sixteenth day, following weight gain of 3 Kg. and sodium retention of 536 mEq. Urinary sodium excretion then assumed a cyclical pattern with peaks of excretion and retention every 4 to 5 days. Subject W. M., during the remaining 9 days of aldosterone administration, retained an additional 181 mEq. of sodium but during two days excreted more sodium than during the average control day. Subject T. A., during the remaining 10 days, excreted 73 mEq. of sodium in excess of the expected control excretion for that period. As compared to the average daily control excretion, cumulative electrolyte changes during the entire period of aldosterone administration for W. M. were plus 16.0 Gm. nitrogen, plus 451 mEq. sodium, and minus 211 mEq. potassium[5]. For T. A. they were plus 0.3 Gm. nitrogen, plus 463 mEq. sodium and minus 510 mEq. potassium.[5] Prompt sodium excretion and potassium retention followed omission of aldosterone.

The salivary sodium: potassium ratio was reduced during the treatment period, chiefly due to decreased sodium concentration; there was no change when urinary sodium excretion increased.

There was no significant change in serum sodium or potassium concentrations. Stool electrolyte changes suggest reduced intestinal sodium loss in W. M. and increased potassium loss in T. A.

Effect on urinary steroid excretion

17-Ketosteroid and 17-hydroxycorticosteroid excretion was essentially unchanged during the entire study. Urinary excretion of aldosterone averaged 200 μg. and 100 μg. per 24 hours when 6 and 3 mg., respectively, of the *d,l*-aldosterone 21-monoacetate were administered.

[5] Potassium was corrected for nitrogen with an assumed K/N ratio of 2.7.

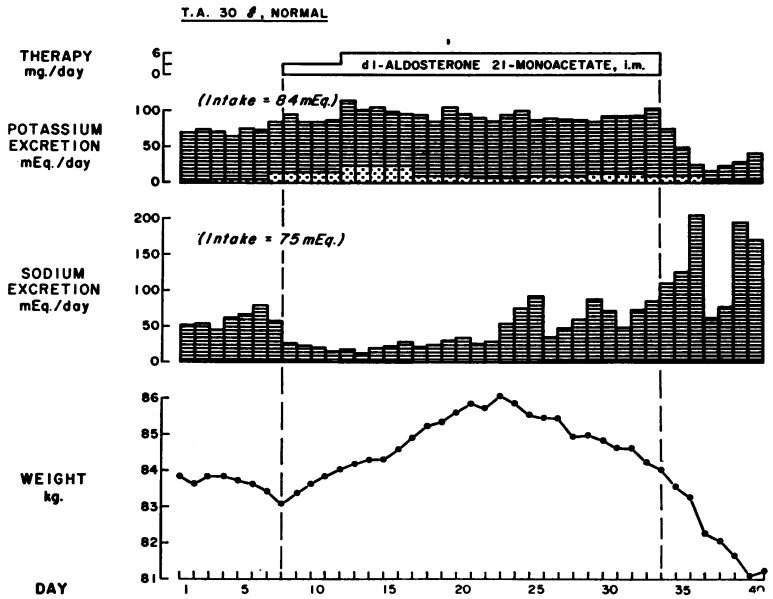

FIG. 2. THE EFFECT OF ALDOSTERONE ON WEIGHT AND SODIUM AND POTASSIUM EXCRETION IN NORMAL SUBJECT T. A. RECEIVING A CONSTANT DIET

Stool electrolyte excretion is indicated by the stippled areas and urinary electrolyte excretion by the cross-hatched areas. Where stippled areas are not seen, the stool electrolyte excretion was less than 1 mEq./day. An escape from sodium retention occurred on the sixteenth day of aldosterone administration.

TABLE I

Metabolic data on Subject W. M.

Day	Body wt.	Urine				Blood				Stool			Saliva		Therapy Aldosterone
		Volume	Na	K	N	Na	K	Hct.*	BUN†	Na	K	N	Na	K	
	Kg.	*ml./day*	*mEq./day*		*Gm./day*	*mEq./L.*		*%*	*mg. %*	*mEq./day*		*Gm./day*	*mEq./L.*		*mg./day*
1	64.43	3,440	133	81	16.0	138	4.1	50.5	15	0.4	8.0	1.5	17	21	0
2	64.66	2,800	93	97	15.2					0.4	8.0	1.5	22	23	0
3	64.55	2,470	102	92	18.2	138	4.3	49.5	16	1.5	7.5	1.5	21	24	0
4	64.89	3,380	135	81	19.7					1.5	7.5	1.5	19	22	0
5	64.89	3,520	130	93	18.6					1.5	7.5	1.5	21	22	0
6	64.43	2,920	99	94	17.9	137	4.3	50.5	15	1.5	7.5	1.5	20	23	0
7	64.66	2,580	60	96	20.5					0.3	9.7	1.6	19	23	3
8	64.66	2,860	28	106	17.4	136	3.9	49.0	14	0.3	9.7	1.6	16	24	3
9	66.59	2,800	31	101	17.1					0.3	9.7	1.6	9	25	3
10	65.91	3,320	75	116	16.9	140	4.0	45.0	13	0.3	9.7	1.6	12	27	3
11	66.25	3,840	104	109	18.2					0.2	7.9	1.7	13	27	3
12	66.36	3,340	83	113	17.4					0.2	7.9	1.7	13	24	3
13	66.36	2,740	46	95	14.9	141	4.0	45.5	11	0.2	7.9	1.7	13	27	3
14	67.05	3,560	79	106	15.8					0.2	7.9	1.7	9	26	3
15	67.05	3,220	104	99	14.6	142	3.8	45.5	11	0.3	8.0	1.9	12	26	3
16	67.16	3,720	71	99	13.4					0.3	8.0	1.9	14	24	3
17	67.95	2,730	94	94	16.2	144	3.9	45.0	11	0.3	8.0	1.9	9	25	3
18	65.50	3,440	115	98	14.8					0.3	8.0	1.9	10	27	3
19	67.50	3,280	143	83	15.8	142	3.8	44.0	12	1.2	6.0	1.4	10	28	3
20	67.95	3,680	138	109	15.1					1.2	6.0	1.4	9	26	3
21		4,560	314	46	17.6					1.2	6.0	1.4	9	26	0
22	66.59	4,040	280	54	15.6	144	4.0	46.0	13	1.2	6.0	1.4	14	22	0
23	65.80	2,970	162	53	15.1					1.7	8.4	1.2	18	23	0
24	65.34	2,920	175	69	20.1	141	5.2	51.0	15	1.7	8.4	1.2	18	22	0
25	65.23														

* Hematocrit.
† Blood urea nitrogen.

TABLE II

Metabolic data on Subject T. A.

Day	Body wt.	Urine				Blood				Stool			Saliva		Therapy Aldosterone
		Volume	Na	K	N	Na	K	Hct.*	BUN†	Na	K	N	Na	K	
	Kg.	*ml./day*	*mEq./day*		*Gm./day*	*mEq./L.*		*%*	*mg. %*	*mEq./day*		*Gm./day*	*mEq./L.*		*mg./day*
1	83.86	1,260	52	67	10.7	139	4.0	46	15	0.3	3.0	0.5	30	18	0
2	83.63	1,120	54	70	16.3					0.3	3.0	0.5	39	18	0
3	83.86	1,080	45	68	14.1					0.2	4.0	0.5	39	18	0
4	83.86	1,140	63	61	15.6	140	3.9	47	13	0.2	4.0	0.5	31	19	0
5	83.75	1,160	66	73	15.0					0.2	4.0	0.5	35	18	0
6	83.63	1,180	79	69	14.6					0.2	4.0	0.5	33	18	0
7	83.45	978	57	81	15.3	138	4.3	43	15	0.2	4.0	0.5	38	20	0
8	83.09	1,190	26	81	14.4					0.2	14.0	2.1	39	20	3
9	83.40	1,070	23	70	14.6	142	3.7	44	14	0.2	14.0	2.1	36	20	3
10	83.63	790	21	71	14.0					0.2	14.0	2.1	32	21	3
11	83.86	1,120	16	73	14.7	138	3.6	44	15	0.2	14.0	2.1	26	22	3
12	84.09	1,100	16	92	14.5					0.7	24.0	2.2	25	21	6
13	84.20	1,020	12	77	13.7	138	4.0	43	12	0.7	24.0	2.2	19	23	6
14	84.30	980	18	82	14.8					0.7	24.0	2.2	23	22	6
15	84.32	1,120	21	74	13.9	137	3.5	43	10	0.7	24.0	2.2	18	21	6
16	84.60	1,100	27	68	14.7					0.7	24.0	2.2	20	23	6
17	84.90	960	22	85	12.8					0.1	7.0	0.9	21	22	6
18	85.22	920	24	76	12.0	136	3.4	42	7	0.1	7.0	0.9	20	23	6
19	85.34	1,150	30	99	13.2					0.1	7.0	0.9	22	23	6
20	85.60	1,030	34	89	12.8	137	3.2	41	9	0.1	7.0	0.9	18	23	6
21	85.86	1,160	26	74	12.9					0.1	6.0	1.0	20	23	6
22	85.72	940	28	78	13.3	143	3.3	40	11	0.1	6.0	1.0	21	23	6
23	86.09	1,740	54	89	12.5					0.1	6.0	1.0	21	21	6
24	85.86	1,760	74	93	12.8					0.1	6.0	1.0	21	20	6
25	85.56	1,280	91	77	12.0	144	3.5	40	8	0.3	10.0	1.3	21	23	6
26	85.45	1,600	34	81	14.1					0.3	10.0	1.3	23	23	6
27	85.45	1,060	47	78	13.3	144	3.4	40	10	0.3	10.0	1.3	17	23	6
28	84.95	1,140	58	78	13.6					0.3	10.0	1.3	17	22	6
29	85.00	1,520	87	72	13.1	144	3.2	41	11	0.3	13.0	0.9	20	25	6
30	84.88	1,260	71	80	13.2					0.3	13.0	0.9	18	24	6
31	84.64	1,340	47	69	14.0					0.3	13.0	0.9	17	23	6
32	84.65	1,420	73	79	14.0	139	4.0	41	8	0.3	13.0	0.9	12	24	6
33	84.22	1,560	85	95	14.0					1.4	9.0	1.6	14	23	6
34	84.04	1,685	109	66	14.2	140	3.0	41	8	1.4	9.0	1.6	17	24	0
35	85.59	1,440	125	39	13.7					1.4	9.0	1.6	23	22	0
36	85.30	2,220	203	16	13.8	144	3.0	41	10	1.4	9.0	1.6	21	22	0
37	82.27	1,220	59	14	14.5					0.6	3.0	0.6	27	17	0
38	82.09	1,940	75	20	13.5					0.6	3.0	0.6	29	17	0
39	81.64	1,780	193	26	14.2	137	3.6	46	13	0.6	3.0	0.6	29	18	0
40	81.09	1,540	167	38	16.5					0.6	3.0	0.6	40	18	0
41	81.25														

* Hematocrit.
† Blood urea nitrogen.

Effect on renal function

There were no demonstrable differences in the 24 hour creatinine clearances between the control and treatment periods. Urine concentration during Pitressin® stimulation on the days before and after aldosterone administration was greater than 1,000 mOsm. per Kg. of water in both subjects.

DISCUSSION

Long term administration of desoxycorticosterone acetate (DCA) to human subjects has been shown to produce only transient retention of sodium (26–28), but a constant increase in exchangeable sodium of 500 to 700 mEq.. (29). The response to large amounts of aldosterone observed in this study appears to be similar. In two normal subjects maximal weight gains did not exceed 3.5 and 3.0 Kg., sodium and water retention occurred for only a few days, and significant edema did not appear, despite continued administration of 3 and 6 mg. of *d,l*-aldosterone 21-monoacetate daily. The data imply that fluid retention in excess of 3 to 5 L. is not to be expected with primary aldosteronism unless other disease processes in-

terfere with the mechanism responsible for sodium and water excretion following an initial period of retention. One may postulate that such an abnormality may exist in patients with cardiac failure, cirrhosis and nephrosis when these disease states are associated with significant edema. Viewed in this manner, factors other than aldosterone assume great importance in the production of edematous states. When primary aldosteronism occurs in conjunction with these other disease processes prominent fluid retention may be expected to occur. A recent case report of primary aldosteronism and edema invites such an explanation (30).

The mechanism of this "escape" from sodium retention during continued administration of aldosterone or other salt retaining corticosteroids is not completely understood. Changes in volume or electrolyte concentration relationships, acting on the kidneys directly or through hormonal or neural pathways, must be considered. Previous studies indicate that natriuresis during administration of DCA does not occur when sodium is restricted (28, 29). In this study, the renal response to aldosterone was apparently dependent upon either fluid volume increase or sodium retention rather than duration of treatment, as shown by the more rapid return to sodium balance with greater sodium intake. That volume is the more important of the two is indicated by evidence that sodium excretion can be induced despite sodium restriction by extracellular fluid volume expansion with Pitressin® and water (12). The method by which this volume expansion results in increased sodium excretion is unknown. In these experimental subjects it obviously cannot be attributed to inadequate adrenal aldosterone production. A change in the metabolism of aldosterone with increased or more rapid hormone inactivation seems unlikely in view of the constant effect on urinary potassium and salivary sodium excretion. Continued depression of the salivary sodium: potassium ratio during the period of increased urinary sodium excretion demonstrates that other effects of aldosterone remain unchanged. This may represent differences in tissue response to the hormone or the effect of other factors acting on the kidney. Secretion of an adrenal sodium excreting hormone or, in the case of primary aldosteronism, of other corticosteroids which interfere with sodium retention may be implicated (16, 31–33). The role of the kidney in this mechanism is still a subject of debate. Increased glomerular filtration rate during volume expansion has been claimed and disputed, and the significance of any elevation is uncertain. Changes in renal tubular function have been postulated but adequate experimental evidence of such is not available. Several recent reviews are devoted to this subject (34–36).

Several authors have pointed out the seemingly "paradoxical" sodium excretion in cases of primary aldosteronism (14, 15, 37, 38). During administration of either ACTH or hydrocortisone, sodium retention occurred for one to three days, followed by sharp natriuresis while the hormone was being given. One may postulate that this phenomenon is based on the same mechanism responsible for the sodium excretion seen in this study. Patients who have already achieved salt and water balance despite primary aldosteronism, when given adrenocortical hormone, will either not retain sodium or will do so for only one or two days before negative sodium balance compensating for this additional sodium retention occurs. The return to sodium and water balance occurs more quickly than seen in this study because maximal or near maximal fluid retention is already present and the stage is set for sodium excretion. Evidence in favor of this concept is found in the natriuresis following acute expansion of body fluids with saline in prehydrated subjects (39, 40), patients with Cushing's syndrome (41, 42), and subjects pretreated with ACTH or corticosteroids (43, 44).

Expansion of extracellular fluid volume with intravenous saline or Pitressin® and water will lead to diminished aldosterone and increased sodium excretion (11–13, 45); that sodium excretion results from diminished aldosterone has been suggested (11–13). In addition, Wrong has postulated that the 6 to 12 hour delay in sodium diuresis following body fluid expansion may be due to slow disappearance of aldosterone from the circulation (46). This study indicates that these two phenomena need not be related; sodium excretion during volume loading occurs despite continued aldosterone administration.

SUMMARY

1. Two normal subjects were given 3 and 6 mg. of *d,l*-aldosterone 21-monoacetate in sesame oil intramuscularly while on a constant diet.

2. Following an initial period of weight gain and sodium retention, weight gain ceased and sodium excretion returned approximately to control levels, despite continued administration of the hormone.

3. Increased potassium excretion occurred throughout the period of aldosterone administration.

4. These findings are consistent with the lack of edema in primary aldosteronism and demonstrate that sodium excretion during volume loading need not be related to diminished aldosterone secretion.

5. It is postulated that the "paradoxical" sodium excretion seen in cases of primary aldosteronism occurs as a result of the "escape" phenomenon.

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