THE EFFECT OF DOCA ON ELECTROLYTE BALANCE IN NORMAL MAN AND ITS RELATION TO SODIUM CHLORIDE INTAKE*

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It has been widely accepted that intramuscular administration of synthetic 11-desoxycorticosterone acetate (DOCA) causes urinary retention of sodium, chloride and water, and loss of potassium both in normal subjects and in those with adrenocortical insufficiency.[2, 18, 20] There is, however, a paucity of published information concerning many aspects of this question which have an important bearing on the problem of the adrenocortical regulation of fluid, electrolyte, and nitrogen balance. In an effort to elucidate this problem, detailed balance studies have been conducted on normal young adults who were given 20 to 40 mgm. of DOCA intramuscularly for periods of three to eleven days.

METHODS AND MATERIALS

A total of nine balances were done on seven healthy young adults: medical students, house officers, and technicians. Each study consisted of a pre-treatment control period of from three to twelve days, followed by a treatment period of from three to eleven days during which time an oily suspension of DOCA‡ was administered intramuscularly twice daily. In five studies, post-treatment periods of from four to nine days were included; in the other four it was not possible to continue observations past the end of the treatment period. The subjects were allowed to continue their usual activities during the period of study but were instructed to avoid all forms of vigorous exercise. All the studies were carried out in the winter or early spring months, when skin losses through sweating should be minimal. The subjects were fed constant diets which contained only 13-15 mEq. of sodium and 15-20 mEq. of chloride but which were otherwise normal in composition. Potassium content was 61 to 95 mEq. In three studies, no sodium chloride was added to the diets; in three others approximately 180 mEq. of sodium chloride were added to the diet each day by use of a weighed salt shaker. In the remaining three subjects approximately 40 mEq. of sodium chloride were added in the salt shaker and an additional daily increment of approximately 450 mEq. of sodium chloride was administered intravenously, from a calibrated flask, in the form of three liters of isotonic saline solution. Oral fluid intake was held constant in each of these latter cases at between 1500 to 1700 cc. per day, while the intake of

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other subjects who were not receiving intravenous fluid was fixed at 2000 to 3000 cc. per day.

Intake in each case was calculated from the average of two or three analyses of duplicate diets and from the analysis of the saline solutions, when these were used. Output was determined by the analysis of 24-hour urine collections preserved with thymol and chloroform and from the analysis of stools pooled in three- to seven-day periods.

Urine and nitric acid digests of homogenized stools and diets were analyzed for sodium and potassium using an internal standard flame photometer. Determinations of chloride,[31] nitrogen,[1] phosphorus,[6] titratable acid,[18] ammonia,[7] and pH (glass electrode) were made on every urine specimen. All urines were acid and no attempt was made to prevent loss of carbon dioxide from the urine as it was collected. Each morning the fasting subjects were weighed on a beam-type balance to the nearest 10 grams. Every few days a sample of venous blood was withdrawn without stasis in an oiled syringe and determinations made of the serum concentrations of sodium and potassium, chloride,[31] and total carbon dioxide content.[30] In some cases whole blood pH was measured with the glass electrode and in the others serum pH was measured colorimetrically.[11]

The daily balance was calculated as net intake minus combined output in stool and urine. No liquid or unusually bulky stools were passed by any of the subjects in this study and daily fecal losses were assumed to be essentially constant within each collection period. The quantity of each substance determined in the pooled stool collections was therefore divided by the number of days in the collection period to obtain an average daily output. Changes in the volume of the "chloride space" and shifts of sodium and potassium into or out of intracellular water were calculated in the usual manner[16] on the assumption that "chloride space" is essentially equivalent to the volume of extracellular fluid and that the latter constituted 20% of the body weight at the beginning of each study.

Results

1. *General effects.* In all three of the subjects on high salt intake and in two of the three subjects on moderate salt intake, administration of DOCA produced an initial increase in weight which was most rapid in the high salt group. When treatment was continued for more than a week, the curve of weight gain tended to level off or to decline. A few subjects receiving salt developed mild peripheral edema. Two who were on high salt intakes showed occasional slight elevation of arterial diastolic pressure but there were no significant blood pressure changes in any of the others. Beginning several days after the initiation of treatment the majority of subjects complained of one or more symptoms including malaise, headache, anorexia, insomnia, and muscle cramps. In some cases these symptoms were severe enough to interfere with the optimal performance of daily tasks.

2. *Effects on urine electrolytes, nitrogen, and acidity.* The detailed balance data obtained from subject M. S., on a low salt intake, subject R. R., on a moderate salt intake, and subject B. Z., on a high salt intake, are presented in Tables 1, 2, and 3 respectively. The results obtained in each of these experiments are typical of those obtained for each of the three dietary groups.

M.S. ♀ 24

TABLE 1

Day	Medications	Body weight	Intake					Urine									Stool				Serum				
			H_2O	Na	K	Cl	N	Vol.	Na	K	Cl	P	NH_4	T.A.	N	pH	Na	K	Cl	N	pH	CO_2	Na	K	Cl
		kg.	cc.	mEq.	mEq.	mEq.	gms.	cc.	mEq./day	mEq./day	mEq./day	mM./day	mEq./day	mEq./day	gms./day		mEq./day	mEq./day	mEq./day	gms./day		mEq./l.	mEq./l.	mEq./l.	mEq./l.
1		62.72	2110	14	64	15	12.2	2007	21	60	23	24	42	26	15.7	6.02	.1	2.0	.2	0.2		26	139	4.8	102
2		62.43	2110	14	64	15	12.2	1982	6	62	11	24	40	27	14.1	5.93	.1	2.0	.2	0.2					
3		62.42	2110	14	64	15	12.2	1897	4	53	11	24	45	27	13.5	5.59	.1	2.0	.2	0.2	7.31	27.5	139	4.5	102
4		62.39	2110	14	64	15	12.2	1822	4	60	8	25	43	26	12.9	5.87	.1	2.0	.2	0.2					
5	DOCA 20 mg.	62.11	2110	14	64	15	12.2	1905	2	55	7	23	43	28	14.1	5.77	.1	2.6	.3	0.3		27.5	139	4.5	103
6	DOCA 20 mg.	61.86	2110	14	64	15	12.2	1900	2	58	6	23	40	26	12.9	5.82	.1	2.6	.3	0.3					
7	DOCA 20 mg.	61.64	2110	14	64	15	12.2	1920	2	53	4	24	45	26	13.6	5.62	.1	2.6	.3	0.3	7.36	28.5	139	4.2	102
8	DOCA 20 mg.	61.62	2110	14	64	15	12.2	2175	2	64	7	25	40	21	13.5	5.89	.1	2.6	.3	0.3					
9	DOCA 20 mg.	61.45	2110	14	64	15	12.2	1965	2	58	5	22	40	19	13.8	5.90	.1	2.6	.3	0.3					
10	DOCA 20 mg.	61.60	2110	14	64	15	12.2	1965	2	46	4	22	43	24	13.4	5.87	.1	2.6	.3	0.3	7.33	29.0	137	4.2	103
11	DOCA 20 mg.	61.49	2110	14	64	15	12.2	1870	1	51	4	19	35	22	12.3	5.97	.1	2.6	.3	0.3					
12	DOCA 20 mg.	61.58	2110	14	64	15	12.2	1755	1	53	5	20	36	22	12.1	5.92	.1	2.6	.3	0.3	7.33	29.0	137	4.0	102
13	DOCA 20 mg.	61.49	2110	14	64	15	12.2	1555	1	54	5	20	35	21	11.8	5.88	.1	2.6	.3	0.3					
14	DOCA 20 mg.	61.57	2110	14	64	15	12.2	1522	1	50	3	20	36	22	12.9	5.66	.1	2.6	.3	0.3	7.37		137	4.3	104
15	DOCA 20 mg.	61.47	2110	14	64	15	12.2	1450	1	51	4	19	32	20	11.7	5.99	.1	2.6	.3	0.3					
16		61.22																			7.36	29.5	137	4.3	104

R.R. ♂ 24.

TABLE 2

Day	Medications	Body weight	Intake					Urine									Stool				Serum				
			H_2O	Na	K	Cl	N	Vol.	Na	K	Cl	P	NH_4	T.A.	N	pH	Na	K	Cl	N	pH	CO_2	Na	K	Cl
									mEq./	mEq./	mEq./	mM./	mEq./	mEq./	gms./		mEq./	mEq./	mEq./	gms./		mEq./	mEq./	mEq./	mEq./
		kg.	cc.	mEq.	mEq.	mEq.	gms.	cc.	day	day	day	day	day	day	day		day	day	day	day		l.	l.	l.	l.
1		68.84	3000	214	61	219	12.5	1860	108	71	131	28	57	32	14.5	6.3	.3	6.1	.3	0.8	7.40	32.0			
2		69.48	3000	214	61	219	12.5	2770	159	68	177	26	50	28	13.6	6.4	.3	6.1	.3	0.8	7.39	29.5	145	3.7	99
3		69.20	3000	214	61	219	12.5	2910	275	52	256	27	48	22	15.1	6.6	.3	6.1	.3	0.8	7.38	27.5	143	3.9	100
4		68.48	3000	214	61	219	12.5	2640	199	50	194	27	51	22	14.3	6.7	.3	6.1	.3	0.8					
5		68.30	3000	214	61	219	12.5	3120	255	56	257	29	52	30	13.9	6.1	.3	6.1	.3	0.8	7.42	29.5			102
6	DOCA 20 mg.	67.79	3000	214	61	219	12.5	3065	150	82	182	28	47	27	13.9	6.45	.2	6.7	.5	0.7					
7	DOCA 20 mg.	67.26	3000	214	61	219	12.5	2350	91	89	120	33	59	34	16.0	6.4	.2	6.7	.5	0.7	7.37	29.5	141	3.8	101
8	DOCA 20 mg.	68.00	3000	214	61	219	12.5	2900	144	89	179	27	56	24	14.1	6.5	.2	6.7	.5	0.7					
9	DOCA 20 mg.	68.00	3000	214	61	219	12.5	2980	142	77	162	27	53	22	13.3	6.6	.2	6.7	.5	0.7	7.40	29.5	142	3.3	101
10	DOCA 20 mg.	67.98	3000	214	61	219	12.5	2900	217	93	248	34	60	21	14.6	6.05	.2	6.7	.5	0.7					
11	DOCA 20 mg.	67.69	3000	214	61	219	12.5	2580	148	77	163	32	54	22	13.5	6.45	.2	6.7	.5	0.7	7.40	30.0	143	3.2	102
12	DOCA 30 mg.	68.05	3000	214	61	219	12.5	3100	222	70	247	25	51	13	10.7	6.65	.2	6.7	.5	0.7			143	3.0	
13	DOCA 30 mg.	67.54	3000	214	61	219	12.5	3770	292	97	307	35	71	23	15.6	6.7	.9	11.6	.5	1.2					
14	DOCA 30 mg.	66.35	3000	214	61	219	12.5	3000	162	72	193	33	75	29	13.7	65	.9	11.6	.5	1.2	7.37	31.0	143	3.0	100
15		66.20	3000	214	61	219	12.5	2490	183	30	146	24	56	15	13.6	6.8	.9	11.6	.5	1.2	7.40	32.0	143	2.8	100
16		66.29	3000	214	61	219	12.5	2770	236	15	180	19	37	9	11.4	6.9	.9	11.6	.5	1.2					
17		66.35	3000	214	61	219	12.5	2270	183	17	177	18	50	17	11.1	6.55	.9	11.6	.5	1.2	7.42	27.5	144	3.5	103
18		66.36	3000	214	61	219	12.5	3700	344	24	342	29	69	21	7.4	6.45	.9	11.6	.5	1.2					
19		65.44																							

In patient M. S., on low salt intake, (Table 1), administration of DOCA for 11 days produced no significant change in the renal excretion of any of the measured electrolytes. In the other two patients (Tables 2 and 3) there was a prompt reduction in excretion of sodium and chloride with a concomitant urinary loss of potassium. In these cases and in all the other subjects on the moderate and high salt intakes, the reduction in sodium excretion exceeded the decrease in chloride. Sodium retention was initially much greater than the urinary potassium loss, and tended to diminish progressively. Usually within a week after treatment with DOCA had begun, urinary sodium and chloride excretion were equal to, or greater than, the control levels, although the potassium diuresis persisted. A more detailed description and analysis of the changes in sodium, chloride, and potassium balance will be presented in Section 5. It is worth noting here, however, that in none of the three subjects with moderate salt intakes and normal urine volumes did treatment with DOCA reduce urine sodium concentration to the levels often observed during physiological states demanding sodium retention. The minimum urine sodium concentration during the administration of DOCA was 24 to 50 mEq./L.

In subjects R. R. (Table 2), B. Z. (Table 3), and in all the others receiving added salt, there was a small but definite rise in daily ammonia excretion which appeared within a few days after treatment had been started. The mean increment in ammonia excretion averaged 8 mEq./day for the subjects on moderate salt intake and 14 mEq./day for those on high salt intake. The maximum increment in ammonia excretion above the largest control value was 13-30 mEq./day for the subjects on high salt intake, and 11-18 mEq./day for the subjects on moderate intake. In the three patients on medium salt intake in whom post-treatment observations were made, ammonia excretion promptly returned to normal. A compensatory "rebound" occurred in only one patient (R. R.). These changes were apparently independent of urine pH, which did not change significantly. In one subject on low salt intake, R. R., there was a small transient increase of ammonia excretion at the inception of treatment, but there were no changes in the other two subjects, V. B. and M. S.

Urinary excretion of nitrogen, phosphorus, and titratable acidity was essentially unaffected by administration of DOCA in all subjects.

3. *Stool composition.* The average daily fecal excretion of sodium, potassium, and chloride for each group of three subjects before, during, and after treatment with DOCA is summarized in Table 4. These data are difficult to interpret because of the limited number of collection periods and the small quantities of electrolyte involved. The data suggest, however, that treatment with DOCA reduced stool sodium content in the high salt group and increased stool potassium content in all subjects. No changes in chloride content were discernible. It is of interest to note that during the

B.Z. ♂ 27.

TABLE 3

Day	Medications	Body weight	Intake					Urine									Stool				Serum				
			H_2O	Na	K	Cl	N	Vol.	Na	K	Cl	P	NH_4	T.A.	N	pH	Na	K	Cl	N	pH	CO_2	Na	K	Cl
		kg.	cc.	mEq.	mEq.	mEq.	gms.	cc.	mEq./day	mEq./day	mEq./day	mM./day	mEq./day	mEq./day	gms./day		mEq./day	mEq./day	mEq./day	gms./day		mEq./l.	mEq./l.	mEq./l.	mEq./l.
1		73.75	4600	474	72	483	14.3	3510	439	64	425	28	50	21	12.6	6.3	2.3	4.8	.8	1.2					
2		73.55	4600	474	72	483	14.3	3755	463	51	467	21	55	14	13.1	6.2	2.3	4.8	.8	1.2	7.36	26.5	145	3.8	107
3		73.20	4600	474	72	483	14.3	4000	510	54	520	21	56	17	12.4	6.0	2.3	4.8	.8	1.2					
4		72.97	4300	498	72	507	14.3	3310	404	46	420	17	51	21	12.6	6.1	2.3	4.8	.8	1.2	7.37	25.5	143	3.8	107
5	DOCA 20 mg.	73.09	4600	477	72	486	14.3	3290	313	63	365	17	49	33	12.0	5.4	1.2	5.9	.9	1.1	7.40	26.5	145	3.8	106
6	DOCA 20 mg.	73.02	4600	481	72	490	14.3	2520	277	82	325	26	57	29	13.4	6.2	1.2	5.9	.9	1.1		27.5	144	3.3	106
7	DOCA 20 mg.	74.16	4534	472	72	481	14.3	3520	358	93	439	24	62	29	13.7	5.9	1.2	5.9	.9	1.1					
8	DOCA 20 mg.	74.60	4600	481	72	490	14.3	3380	345	101	418	25	60	25	14.5	6.2	1.2	5.9	.9	1.1	7.43	30.0	142	3.3	105
9	DOCA 20 mg.	75.15	4600	481	72	490	14.3	3670	414	88	498	23	63	25	13.6	6.1	1.2	5.9	.9	1.1	7.45	31.0	146	3.2	103
10	DOCA 20 mg.	75.30	4600	481	72	490	14.3	3990	460	92	517	28	68	24	14.0	6.3	1.2	5.9	.9	1.1					
11	DOCA 20 mg.	75.32	4600	470	72	479	14.3	2980	429	54	454	22	87	10	14.5	6.5	1.2	5.9	.9	1.1	7.39	32.0	143	2.9	104
12		76.01																			7.38	31.0	146	2.8	103

control periods, stool sodium content was lowest in the subjects on low-salt diets.

4. *Serum electrolytes.* Serum potassium concentration decreased in every subject given moderate or large amounts of salt but did not change

TABLE 4
CHANGES IN STOOL ELECTROLYTE

	Low Na intake	*Medium Na intake*	*High Na intake*
		Average stool sodium, mEq./day	
Control	0.1	0.5	1.9
DOCA	0.1	0.4	0.8
Post-treatment	0.2	0.9	..
		Average stool potassium, mEq./day	
Control	3.7	6.9	5.2
DOCA	4.5	8.2	7.5
Post-treatment	5.3	8.8	..
		Average stool chloride, mEq./day	
Control	0.5	0.4	0.8
DOCA	0.6	0.4	0.9
Post-treatment	0.3	0.5	..

TABLE 5
CHANGES IN SERUM POTASSIUM

	Diet		*Serum K mEq./L.*		
Subject	*mM. NaCl per day*	*Days of DOCA*	*Initial*	*End of DOCA*	*Maximum post-treatment*
A. L.	530	5	4.5	3.7	...
E. A.	535	3	4.5	3.4	...
B. Z.	480	7	3.8	2.8	...
R. R.	214	9	3.9	2.8	...
E. A.	191	9	4.2	3.6	5.0
A. M.	182	10	4.4	3.6	5.3
R. R.	13	8	3.7	3.7	4.0
V. B.	15	9	3.8	4.1	4.0
M. S.	14	11	4.5	4.3	4.3

in the other three. These changes are summarized in Table 5. The reduction in potassium concentration in the subjects receiving salt was from .6 to 1.1 mEq. per liter, with no significant difference between the high and medium salt groups. In two of the three patients who were adequately studied in the post-treatment period (all on medium salt intakes), serum

potassium rose above the highest control value. In all but one of the subjects there were no changes in CO_2 content or chloride concentration in the serum and in none did the blood pH or serum sodium vary significantly. In one of the subjects (B. Z., Table 3) on a high salt intake, DOCA administration was accompanied by a rise of 4 mEq./liter in carbon dioxide content and an equivalent reduction in chloride.

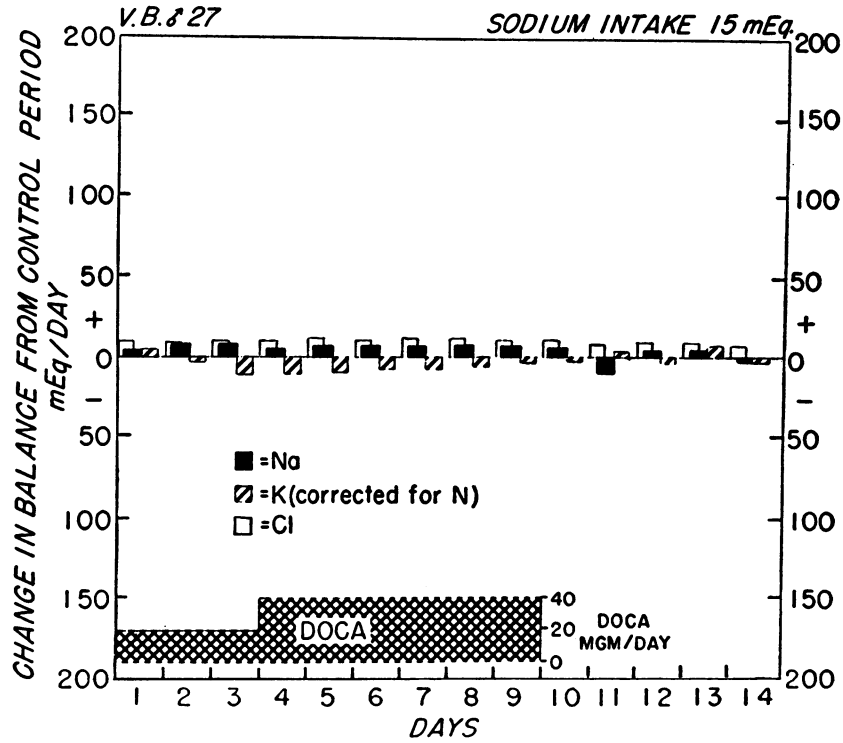

FIG. 1

Figures 1-9 show the changes in sodium, chloride, and potassium balances during and, in some instances, following DOCA administration. Values have been obtained by algebraically subtracting the average control daily balance from the daily balance during the treatment and post-treatment periods.

5. *Sodium chloride and potassium balances.* In Figures 1-9 are depicted the changes effected by DOCA in the net balances of sodium, chloride, and potassium (the latter was corrected for changes in nitrogen balance with an assumed K : N ratio of 2.7 mEq. K/gm. N). The data for these charts were obtained by algebraically subtracting the average control daily balance from the balance for each subsequent day. This can be assumed to correct for any systematic methodological error and for constant skin losses of electrolytes.

From Figures 1-3 it can clearly be seen that treatment of the three patients on a low-salt diet with 20 or 40 mgm. of DOCA per day for eight to eleven

days produced a small retention of sodium and chloride and only a small variable loss of potassium. In subject V. B. (Fig. 1) the potassium diuresis tended to decrease with continued treatment. In subject R. R. (Fig. 2) there was no change in potassium balance after three days of treatment with 20 mgm. of DOCA/day, but on the fourth and fifth days after the dose was

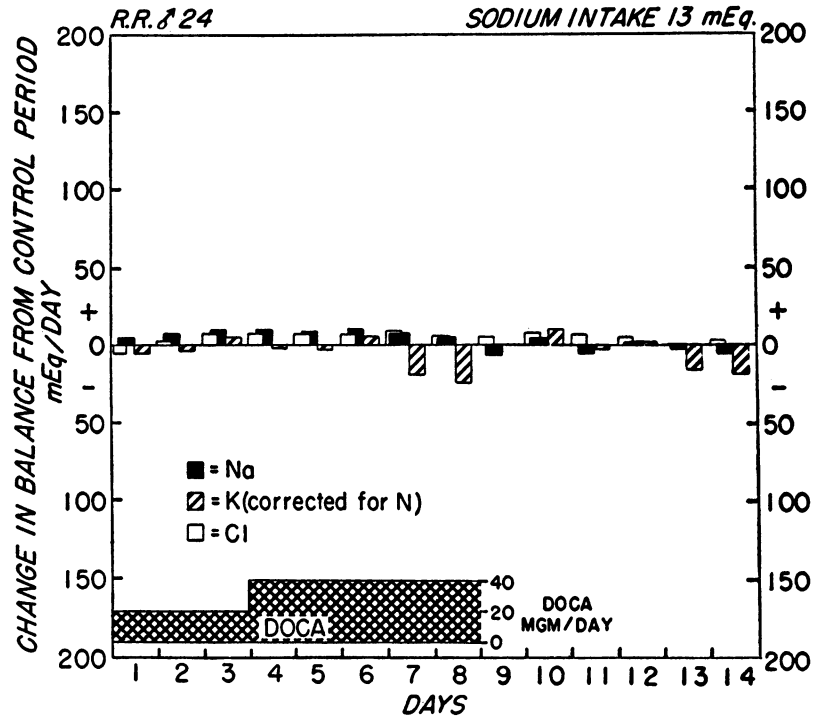

FIG. 2

doubled, small but probably significant potassium losses occurred. In neither of these latter two subjects was there any significant retention of potassium or loss of sodium in the post-treatment period.

In sharp contrast with the above results were the large changes in electrolyte balance observed in the six subjects given salt. In Figures 4-9 it may be seen that in each case DOCA produced an immediate retention of sodium and chloride and a loss of potassium. The large initial retentions of sodium and chloride quickly diminished, however, and usually by the end of a week daily sodium and chloride balance had returned to control levels or were actually negative. The total amount of sodium and chloride retention defined by these charts appeared to be proportional to the sodium intake, since the largest positive balance changes were seen in the subjects given large amounts of salt (Figs. 7-9).

By contrast, the loss of potassium in excess of nitrogen continued unabated in most cases for as long as the hormone was given. In subjects E. A. (Fig. 4) and B. Z. (Fig. 7), however, the potassium balance became reversed on the ninth and seventh days of treatment, respectively.

TABLE 6

CHANGES IN POTASSIUM BALANCE FROM CONTROL PERIOD (CORRECTED FOR NITROGEN)

Subject	*Days*	*Total for period mEq.*	*Average daily mEq.*
High salt intake			
A. L.	5	—92	—18
E. A.	3	—132	—44
B. Z.	6	—191	—32
Moderate salt intake			
R. R.	9	—237	—26
E. A.	8	—172	—22
A. M.	10	—185	—19

TABLE 7

INTERNAL BALANCES

	Salt intake mM. per	*Control*			*DOCA*			*Post-treatment*		
Subject	*day*	*Days*	*ICNa*	*ICK*	*Days*	*ICNa*	*ICK*	*Days*	*ICNa*	*ICK*
A. L.	530	2	+28	—8	5	+21	—133	..	.....	.....
E. A.	535	5	—61	—44	3	+86	—147	..	.....	.....
B. Z.	480	4	—59	+45	7	+145	—88	..	.....	.....
R. R.	214	5	+62	+10	9	+95	—205	4	—81	+94
E. A.	191	5	—189	—47	9	—90	—242	5	—46	+68
A. M.	182	12	—55	+101	10	+112	—114	10	—295	+237

In Table 6 are presented the cumulated and average daily potassium balances during administration of DOCA. These data are derived from Figures 4-9, but the final days in Figures 4 and 7, when potassium balances became positive again, have been omitted. The mean potassium losses averaged 27 mEq./day for the entire group. The daily losses appeared to be slightly greater in the subjects on high salt intake, but this difference is not of statistical significance. The mean total cumulated loss of potassium in excess of nitrogen was 168 mEq. Despite the magnitude of these changes, serum bicarbonate concentration changed in only one subject, and in this case only slightly.

In each of the three subjects on moderate salt intake in whom post-treatment periods were obtained (Figs. 4-6) cessation of treatment with DOCA resulted in a more or less prompt reversal of the initial changes in electrolyte balance.

6. *Internal balances of sodium and potassium.* In general, the changes in external sodium and chloride balance were parallel, but in all except one of

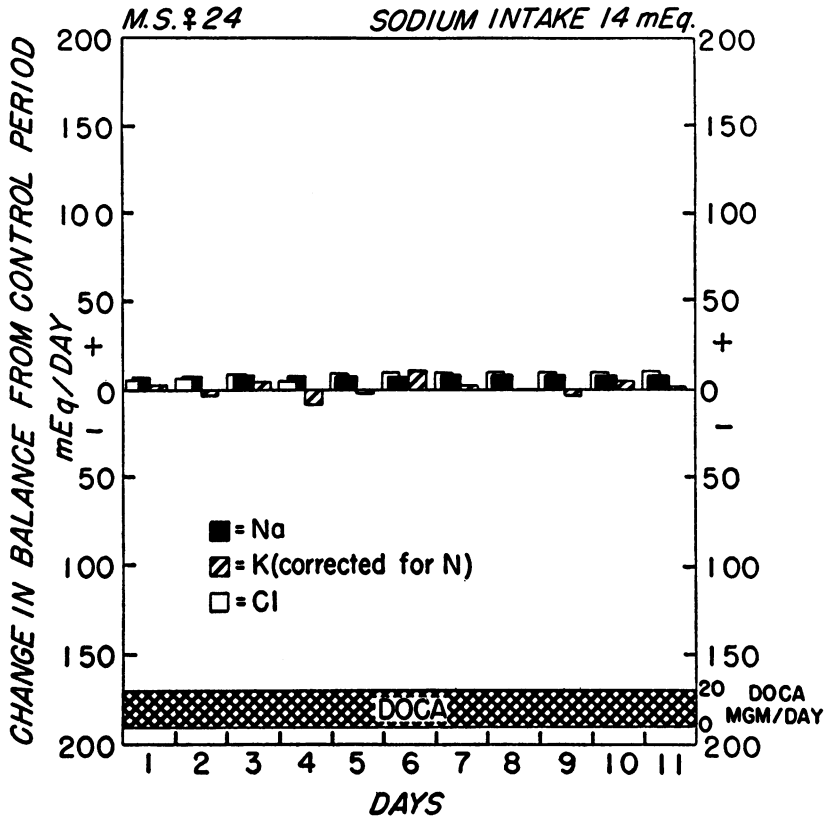

FIG. 3

the subjects receiving added salt (E. A., Fig. 4) the retained sodium exceeded the retention of chloride by more than the ratio of sodium to chloride in extracellular water. Serum concentrations of sodium and chloride were virtually unchanged. Therefore, assuming the extracellular position of chloride, this excessive retention of sodium defines a shift of sodium into intracellular water. On the other hand, the large losses of potassium in excess of nitrogen with only small changes in serum concentration must have resulted from a movement of potassium out of cells.

These changes in internal balance were calculated separately for the periods before, during, and after treatment with DOCA and are sum-

marized in Table 7. It should be noted that these calculations are based on the total cumulated balances for each period and do not refer to the changes in daily balance depicted in Figures 4-9. The tabulated data show that in five of the six subjects given salt, treatment with DOCA caused a shift of sodium into cells of from 21 to 145 mEq., and a simultaneous loss of cellular potassium of from 88 to 205 mEq. There was no apparent quantitative

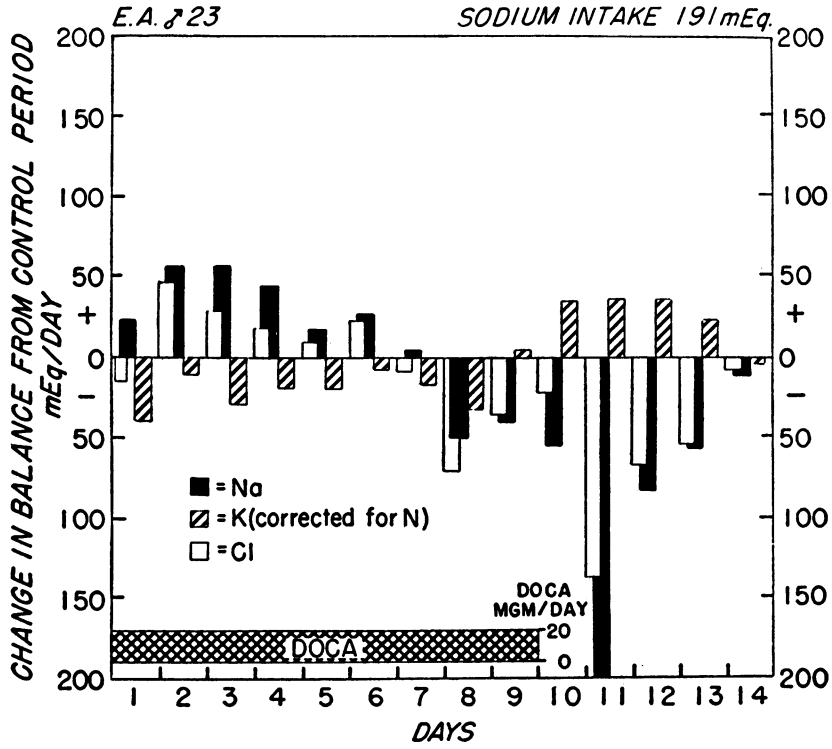

FIG. 4

correlation between the cellular exchanges of sodium and potassium during the treatment period. In the subjects on moderate salt intake followed through a post-treatment period, these changes became approximately reversed.

DISCUSSION

The data presented here afford ample confirmation of the fact that DOCA produces in normal subjects given sodium chloride an initial retention of sodium and chloride and an increased excretion of potassium without change in nitrogen or phosphorus balance. It seems equally clear, however, that with the doses employed here the initial effect on sodium and chloride is only transient and usually disappears within a week despite

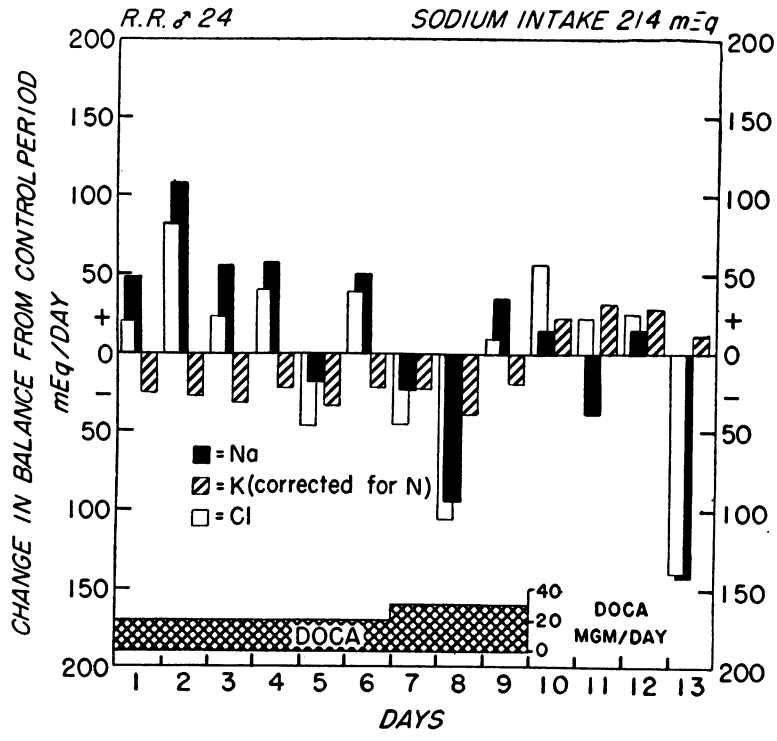
R.R. ♂ 24
SODIUM INTAKE 214 mEq
CHANGE IN BALANCE FROM CONTROL PERIOD
mEq/DAY
200
150
100
50
+
0
−
50
100
150
200
■ = Na
▨ = K(corrected for N)
□ = Cl
DOCA
40
20
0
DOCA
MGM/DAY
1 2 3 4 5 6 7 8 9 10 11 12 13
DAYS

FIG. 5

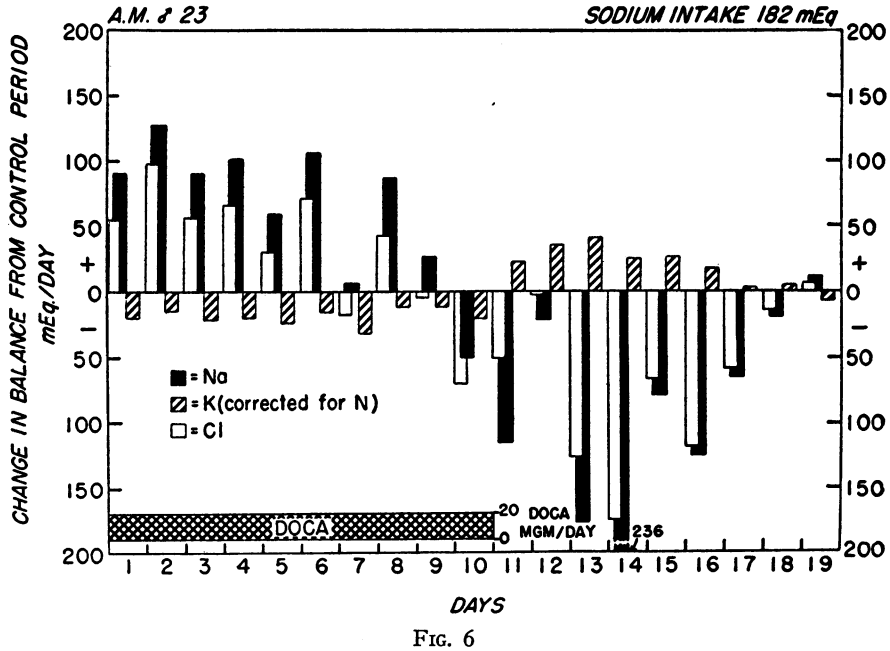
A.M. ♂ 23
SODIUM INTAKE 182 mEq
CHANGE IN BALANCE FROM CONTROL PERIOD
mEq/DAY
200
150
100
50
+
0
−
50
100
150
200
■ = Na
▨ = K(corrected for N)
□ = Cl
DOCA
20
0
DOCA
MGM/DAY
236
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
DAYS

FIG. 6

continued treatment. The potassium diuresis is at first unaffected by the restoration of sodium balance, but in two of our subjects potassium balance was restored to normal on the seventh and ninth days of treatment respec-

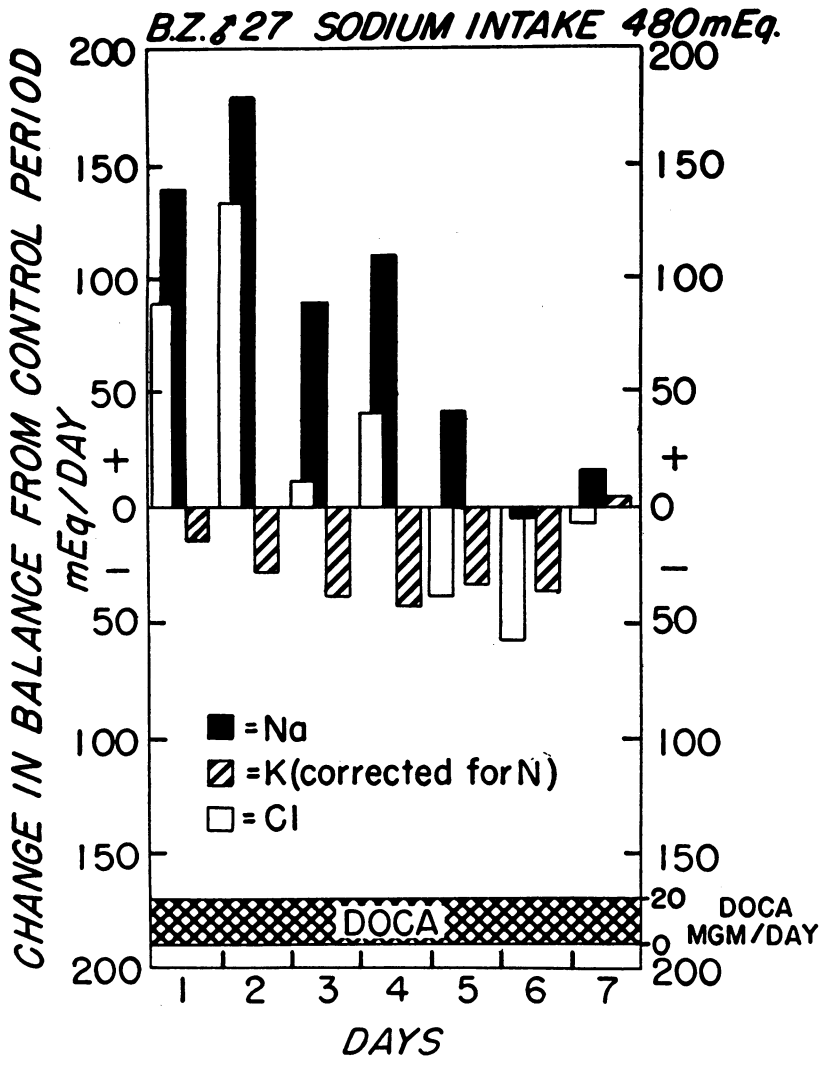

FIG. 7

tively. Similar observations have been made with regard to the transitory influence of DOCA on sodium balance[4, 32] and on sodium and potassium balance.[19] In this respect the action of DOCA on electrolyte balance resembles that of Cortisone[27] and Compound F.[24]

Escape of sodium balance from the initial effects of Cortisone or Compound F might be attributed to induced adrenocortical insufficiency[27]

but there is evidence that treatment of normal men with DOCA in doses comparable to those used here does not inhibit endogenous adrenal steroid production.[4] The absence of any post-treatment sodium diuresis or potassium retention in patients V. B. (Fig. 1) and R. R. (Fig. 2), who were not given salt during the period of study, as well as the persistence of reduced sweat sodium content even after renal "escape" has occurred[8] also argue against the possibility of adrenal inhibition with DOCA. Rapid develop-

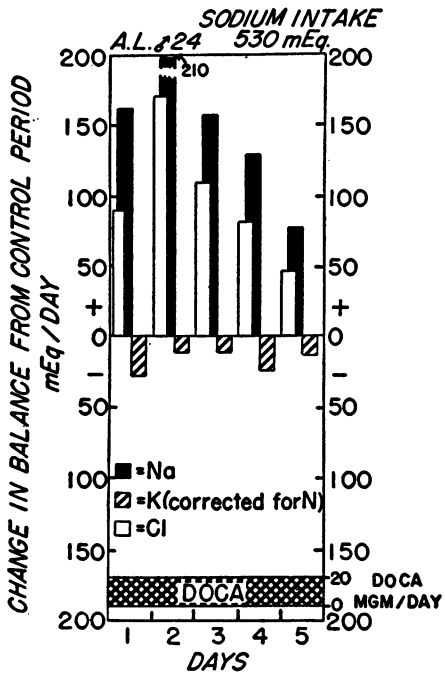

FIG. 8

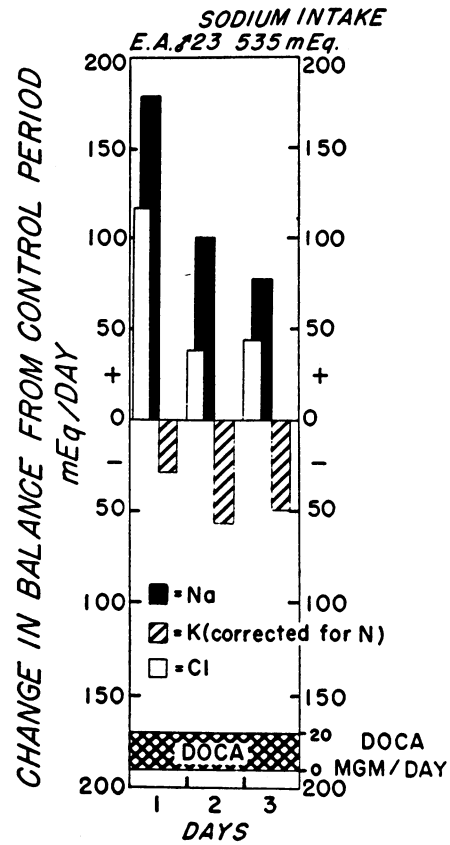

FIG. 9

ment of relative refractoriness to the effects of DOCA by renal tubular cells is a possibility which cannot be evaluated at present, but it must be considered unlikely in view of the fact that DOCA can maintain sodium balance in patients with adrenocortical insufficiency for indefinite periods. It seems more probable that sodium balance was restored by other regulatory mechanisms. These might involve rapid expansion of plasma volume and increase in glomerular filtration rate, changes which usually occur following treatment of normal subjects[5,14] or dogs[9] with salt-retaining adrenal

steroids and which are often associated under other circumstances with increased salt excretion.[21, 26]

The dependence of potassium diuresis upon the level of sodium chloride intake was one of the striking findings in this study. In one subject on a low-salt diet (M. S., Table 1 and Fig. 3) there was absolutely no loss of potassium. This phenomenon has been independently observed by Seldin, Welt, and Cort.[25] In the other two subjects on low-salt diets the losses of potassium were much smaller and less sustained than those observed in all of the six other subjects given added salt. Thus it would appear that the potassium diuresis produced by DOCA is dependent in some way upon sodium chloride intake. Similar conclusions may be drawn from observations on the effects of Compound F.[24]

The continuation of potassium loss for several days after sodium retention had stopped indicates that there is no direct relationship between net retention of sodium and loss of potassium. It is possible, however, that increased potassium excretion depends upon an augmented rate of renal tubular reabsorption of sodium, which continues while DOCA is administered, even after increases in glomerular filtration rate have restored sodium excretion to normal. The smaller, more variable increases in potassium excretion observed in two of the subjects on the low-salt diet may have resulted from the smaller increments in sodium reabsorption permitted under these circumstances. The eventual dissipation of potassium diuresis may be the result of hypokalemia and a diminishing load of potassium delivered to the renal tubules, or else the direct result of renal tubular potassium depletion.

It is of interest to note that relatively large losses of potassium in excess of nitrogen occurred in our subjects without the development of alkalosis. Others have reported that alkalosis may accompany potassium deficits of this magnitude produced by administration of ACTH or Cortisone.[27] This difference cannot be attributed to the relation of dietary chloride to sodium[20] because this was the same in both groups. It would appear either that the difference is due to chance variation in the individual response of the subjects studied or that factors other than potassium depletion are involved in the production of alkalosis with ACTH and Cortisone.

The internal balances summarized in Table 6 show no quantitative relationship between exchanges of sodium and potassium. However, these data must be interpreted with the greatest caution because in only a few instances are the calculated shifts large enough to be of even statistical significance.[28] The direction of the shifts is nevertheless uniform enough to allow the conclusion that during treatment with DOCA cell balances of sodium probably did become positive while corrected potassium balances became negative. It is also worth noting that no significant cellular shifts occurred during the control period in the subjects given large quantities of extra salt as daily saline infusions. Other workers have noted that large

loads of sodium chloride did not increase intracellular sodium content in normal adults[17, 28] or in normal dogs[12] but intracellular Na content was apparently increased by sodium chloride loading in a normal infant studied by Gamble *et al.*[8]

The changes produced in renal ammonia secretion are of considerable significance although they were small and variable. There was no relation between urine acidity and ammonia content. It is of interest, moreover, that ammonia excretion increased in all of the subjects given salt although it was affected, and then but slightly, in only one of the three subjects on a salt-free diet. Others have shown that adrenal insufficiency reduces renal synthesis of ammonia both *in vivo*[10, 15] and *in vitro*[15] and that administration of DOCA or added dietary salt will improve this function in adrenalectomized dogs.[10] Interpretation of these observations must await further study of the factors controlling ammonia production.

Summary and Conclusions

Electrolyte and nitrogen balance studies have been carried out on normal young adults who were given 20 to 40 mgm. of DOCA intramuscularly for periods of three to eleven days.

In six subjects whose diets were supplemented with moderate or large amounts of salt, administration of DOCA produced immediate retention of sodium and chloride, and a loss of potassium. The retention of sodium exceeded that of chloride and was greatest in subjects given the highest salt intake. With continued administration of the hormone, sodium retention diminished, and often a sodium diuresis appeared.

The negative balance of potassium averaged 27 mEq./day. This loss, unaccompanied by change in nitrogen balance, continued beyond the period of sodium retention, and regularly resulted in hypokalemia. The cumulative deficits of potassium ranged from 92 to 237 mEq., and were accompanied by intracellular shifts of sodium. There were no significant changes in serum bicarbonate or chloride concentration.

The three subjects on low sodium diets failed to show the changes in potassium balance described above. In one of these subjects there was no loss of potassium; in another, potassium diuresis did not appear until the seventh day of treatment; in the third subject, loss of potassium was minimal and only transient.

Ammonia excretion increased in all the subjects given salt but rose in only one subject on a low-salt diet. In the latter instance, the change was small and transitory. In no subjects were there significant changes in urine pH, titratable acidity, or in phosphorus excretion.

The observations in this study are consistent with the view that the increased potassium excretion as well as the small increases in ammonia secretion produced by treatment with DOCA are in some way conditioned by the simultaneous augmentation of renal tubular reabsorption of sodium

and chloride. Eventual escape from the sodium-retaining effect of DOCA is probably the result of regulatory mechanisms which override the hormonal effect on the renal tubule.

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