JCI The Journal of Clinical Investigation

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J Clin Invest. 1962;41(2):218-229. https://doi.org/10.1172/JCI104473.

Research Article

Journal of Clinical Investigation
Vol. 41, No. 2, 1962

FACTORS GOVERNING CORRECTION OF THE ALKALOSIS ASSOCIATED WITH POTASSIUM DEFICIENCY; THE CRITICAL ROLE OF CHLORIDE IN THE RECOVERY PROCESS *

By E. LAURENCE ATKINS and WILLIAM B. SCHWARTZ †

(From the Department of Medicine, Tufts University School of Medicine, and the Renal Laboratory, Pratt Clinic-New England Center Hospital, Boston, Mass.)

(Submitted for publication July 21, 1961; accepted September 11, 1961)

Recent observations on the dog indicate that during recovery from chronic hypercapnia the chloride ion plays a critical role in permitting full restoration of plasma composition to normal (1). Plasma bicarbonate concentration remains significantly elevated, and plasma chloride concentration markedly depressed unless chloride is provided in the diet. It was tentatively proposed that when the quantity of chloride available for reabsorption is reduced, the transtubular potential difference generated by active transport of sodium is greater than normal and that this, in turn, is responsible for a higher than normal rate of diffusion of hydrogen ions into the glomerular filtrate and for the sustained elevation of plasma bicarbonate concentration.

The present study was undertaken to determine whether chloride may play a significant role in the correction of the metabolic alkalosis associated with potassium deficiency. For this purpose, studies have been performed in dogs made potassium deficient, alkalotic, and hypochloremic by the administration of deoxycorticosterone acetate (DCA)[1] and sodium bicarbonate. Subsequently, three consecutive maneuvers were carried out while the animals were maintained on a diet low in potassium and chloride: *1*) DCA was withdrawn, *2*) potassium bicarbonate was substituted for sodium bicarbonate in the daily electrolyte supplement, and *3*) chloride was administered in various forms. The data indicate that withdrawal of DCA and administration of potassium bicarbonate resulted in only partial correction of the metabolic alkalosis despite almost total correction of the potassium-deficient state. The major reduction in bicarbonate concentration occurred during the repair of the chloride deficit. This finding is consistent with the hypothesis that the hypochloremia and chloride deficiency exerted a significant effect on the transfer of hydrogen ions into the glomerular filtrate and were responsible for the maintenance of an elevated plasma bicarbonate concentration.

METHODS

Balance studies were carried out on 6 healthy female dogs weighing between 17 and 22 kg. Each day the animals were fed 25 g per kg of a synthetic diet, the composition of which has been described previously (2). The intrinsic electrolyte content of the diet was approximately 1 mEq of sodium per 100 g, 1 mEq of chloride per 100 g, and less than 0.1 mEq of potassium per 100 g. Supplementary electrolytes were added to the diet from stock solutions whose composition had been verified by direct analysis. In most instances, the diet was administered by gastric tube in two portions (a.m. and p.m.). Daily intake values were corrected for the slight amounts remaining in the bottle and tubing. In a few instances the dogs ate spontaneously during the early part of the study, but as severe potassium depletion developed, it became necessary to tube-feed all animals.

Each study was initiated by a control period during which the synthetic diet was administered for a period of at least 1 week. In 5 animals the daily intake was supplemented during this period with 2.5 mEq per kg of sodium, 2.5 mEq per kg of potassium, and 5.0 mEq per kg of chloride. The diet of one of these animals (Dog Y) was further supplemented by the addition of 1.5 mEq per kg per day of phosphate as sodium phosphate (pH 7.4), in order to allow for ready substitution of chloride for phosphate during the last phase of the study (see below). The electrolyte intake in the sixth dog (chronologically the first in the series) differed in several minor respects from that used in the other 5 animals. Although the slight differences in protocol did not appear to affect significantly the pattern of the re-

* Supported in part by grants from the National Heart Institute, National Institutes of Health, Public Health Service (H-759 and HTS-5309), and the Life Insurance Medical Research Fund.

† Established Investigator, American Heart Association.

[1] The authors wish to express their appreciation to Dr. C. H. Sullivan of Ciba Pharmaceutical Products, Inc., for the generous supply of DCA (Percorten).

sults, detailed balance data will not be shown, since direct comparison with the other studies is difficult; only the observations on plasma composition will be presented.

Metabolic observations in each study were begun 4 days before the beginning of Period I (induction of potassium deficiency). The protocols for each period are outlined in detail below.

Period I: Induction of potassium deficiency and alkalosis by administration of DCA and sodium bicarbonate. The supplementary sodium chloride and potassium chloride administered during the control period were replaced by sodium bicarbonate, 5.0 mmoles per kg per day. (In addition, in Dog Y the supplement of sodium phosphate was continued.) A daily injection of 0.5 mg per kg of DCA in oil was given to each animal until plasma bicarbonate concentration had risen to a level of at least 30 mEq per L.

Period II: DCA withdrawal. DCA injections were discontinued but the sodium bicarbonate supplement of 5.0 mmoles per kg per day was maintained until plasma bicarbonate concentration had stabilized for a period of at least 2 days. (In addition, in Dog Y the supplement of sodium phosphate was continued.)

Period III: Replacement of sodium bicarbonate by potassium bicarbonate. The sodium bicarbonate given in Periods I and II was replaced by an equimolar quantity of potassium bicarbonate (5.0 mmoles per kg per day). (In addition, the sodium phosphate supplement in Dog Y was replaced by an equimolar quantity of potassium phosphate.) This regimen was continued until plasma bicarbonate concentration was essentially constant and potassium excretion was virtually equal to potassium intake for a period of at least 2 days. At this time, two dogs, U and W, were given an additional daily quantity of 1.5 mmoles per kg of potassium bicarbonate on 4 successive days in order to assess the effects of a higher potassium intake on plasma bicarbonate concentration and potassium balance. In these animals, a further 3-day period of observation was carried out after the extra potassium intake was discontinued.

Period IV: Administration of chloride. During this final period the potassium bicarbonate intake was continued at the same level as in Period III (5.0 mmoles per kg per day). However, the electrolyte intake was altered in the following ways in order to repair the chloride deficit: *a*) 3 dogs (J, S, T) were given sodium chloride, 2.5 mmoles per kg per day; *b*) 2 dogs (U, W) were given potassium chloride, 1.5 mmoles per kg per day (these two animals were the same ones that had received an equimolar increment of potassium bicarbonate during Period III); *c*) chloride, 1.5 mEq per kg, was substituted for the equivalent amount of phosphate in the diet of one dog, Dog Y (which had received the phosphate supplement). The period of augmented chloride intake was continued until approximate chloride balance and a steady plasma bicarbonate concentration had been achieved for a period of at least 2 days.

Studies were carried out in metabolic cages which permitted the urine to drain over a siliconized tray into bottles containing mineral oil and a thymol-chloroform mixture. The system was tested with water and gave over 97 per cent recovery. The volume, pH, and CO_2 of the urine were determined on each 24-hour specimen promptly after the collection was completed. On most mornings, a 20-ml sample of arterial blood was drawn into a heparinized syringe. Feces were collected and pooled separately for each period and the collections were begun and ended 24 hours later than the corresponding experimental period.

The analytic methods for pH, CO_2 content, sodium, potassium, chloride, and organic acids have been described previously (3, 4). Titratable acid was calculated from the contribution of phosphate, assuming a constant pK'_2 of 6.8, since this introduces an insignificant error when the pH is above 7.00 (3), as was the case in almost all the specimens from the present study. The contribution of organic acids to titratable acidity was ignored since it proved to be negligible over the pH range encountered during the studies. Both plasma creatinine and urine phosphate were determined on the Technicon Autoanalyzer; the former, using a modification of the method described by Chasson, Grady and Stanley (5), and the latter, by an adaptation of the method of Fiske and Subbarow (6). Urine ammonia was determined in the early studies by the Seligson microdiffusion method (7), but in the later studies it was determined on the Autoanalyzer using the method of Logs-

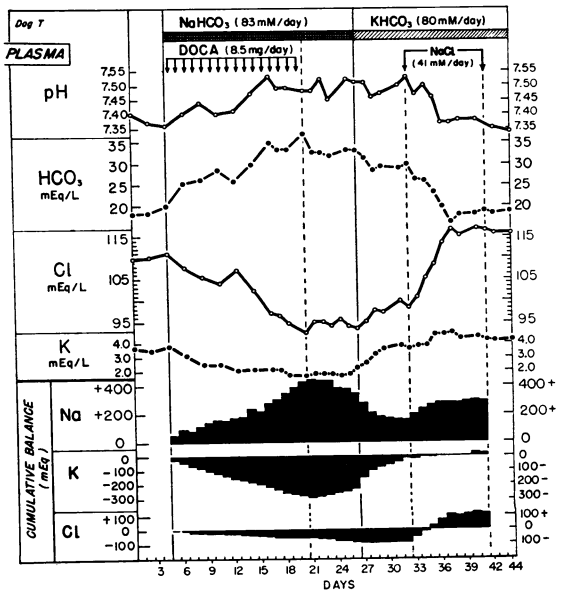

FIG. 1. PLASMA COMPOSITION AND CUMULATIVE ELECTROLYTE BALANCES DURING DEVELOPMENT AND CORRECTION OF ALKALOSIS ASSOCIATED WITH POTASSIUM DEPLETION; CHLORIDE DEFICIT REPAIRED BY ADMINISTRATION OF NaCl (DOG T). The values for potassium balance have been corrected for changes in nitrogen balance (2.7 mEq per g of nitrogen). The values for the electrolyte supplement varied slightly from those shown at the top of the figure (see Table I).

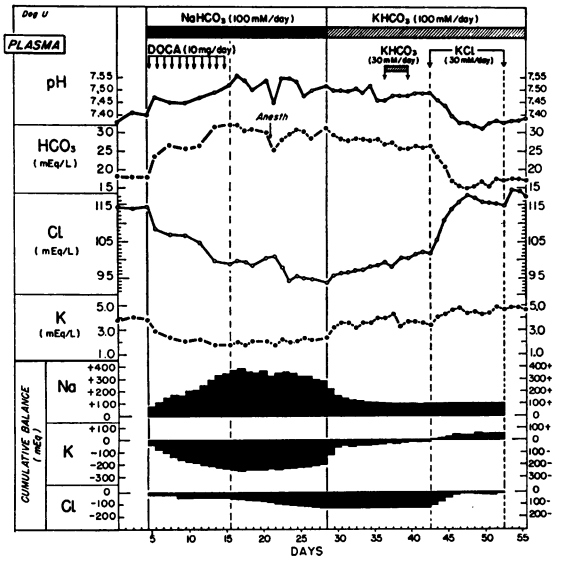

FIG. 2. PLASMA COMPOSITION AND CUMULATIVE ELECTROLYTE BALANCES DURING DEVELOPMENT AND CORRECTION OF ALKALOSIS ASSOCIATED WITH POTASSIUM DEPLETION; CHLORIDE DEFICIT REPAIRED BY ADMINISTRATION OF KCl (DOG U). The transient fall in plasma bicarbonate concentration during Period II followed the use of pentobarbital anesthesia. The values for potassium balance have been corrected for changes in nitrogen balance (2.7 mEq per g of nitrogen). The values for the electrolyte supplement varied slightly from those shown at the top of the figure.

don (8). The electrolyte content of diet, stool, and vomitus was determined on nitric acid extracts. Nitrogen was measured by the Kjeldahl method. The daily balance was calculated as the net intake minus the combined output in the urine, stool, and blood sample. Each 20 ml of blood withdrawn was considered to contain 2 mEq of chloride and 3 mEq of sodium. In calculating a correction for potassium excretion due to changes in nitrogen balance, a value of 2.7 mEq of potassium per g of nitrogen was used. Changes in the volume of the "chloride space" and shifts of sodium and potassium between extra- and intracellular spaces were calculated in the usual manner, on the assumption that chloride is limited to the extracellular compartment. The initial volume of the extracellular fluid was in each instance assumed to be 20 per cent of the body weight.

RESULTS

The principal features of three representative studies are shown in Figures 1 through 3 and complete data from one study are given in Table I. These studies will not be described individually, but will be considered in relation to the collective data for each period.

Period I: Induction of potassium deficiency and alkalosis by administration of DCA and sodium bicarbonate

Acid-base. Plasma bicarbonate concentration rose progressively during the period of DCA administration (Figures 1–3). Mean plasma bicarbonate concentration at the beginning of the period was 19.0 mEq per L (range, 16.7 to 20.4 mEq per L) and at the end was 35.6 mEq per L (range, 32.2 to 40.5 mEq per L), an average rise of 16.6 mEq per L. In association with the increase in bicarbonate concentration, there was a rise in plasma pH to a final range of 7.45 to 7.55 (Figure 4) and also a slight rise in plasma pCO_2 (Figure 4). It is of interest that each of the three dogs whose plasma bicarbonate concentration was measured 1 day after the period was begun showed a rise in concentration on that day which was greater than on any subsequent day.

The changes in acid-base composition of the

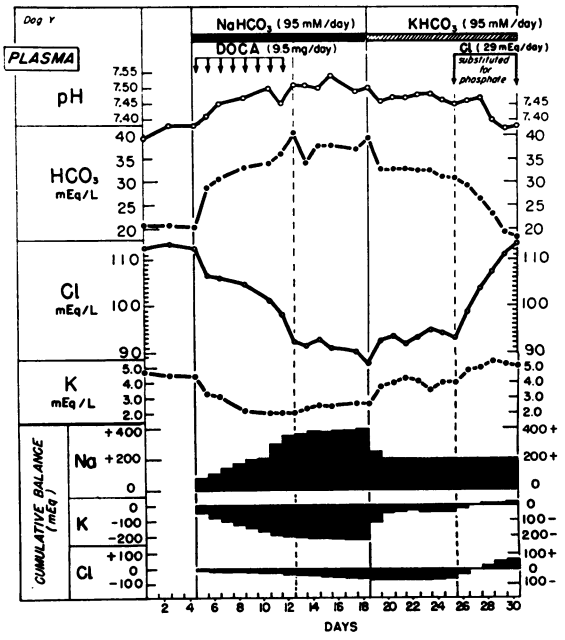

FIG. 3. PLASMA COMPOSITION AND CUMULATIVE ELECTROLYTE BALANCES DURING DEVELOPMENT AND CORRECTION OF ALKALOSIS ASSOCIATED WITH POTASSIUM DEPLETION; CHLORIDE DEFICIT REPAIRED BY SUBSTITUTION OF CHLORIDE FOR PHOSPHATE IN DAILY ELECTROLYTE SUPPLEMENT (DOG Y). The values for potassium balance have been corrected for changes in nitrogen balance (2.7 mEq per g of nitrogen). The values for the electrolyte supplement varied slightly from those shown at the top of the figure.

TABLE I

Balance data on a dog in which chloride deficit was repaired by administration of sodium chloride (Dog T)

		Intake				Urine											Stool				Plasma					
	Day	Body wt	Na	Cl	K	N	Vol	pH	HCO_3	Cl	Na	K	NH_4	T.A.*	PO_4	Organic acids	N	Na	Cl	K	N	pCO_2	pH	HCO_3	Na	Cl	K
		kg	*mEq/day*			*g/day*	*ml/day*		*mEq/day*		*mEq/day*		*mEq/day*		*mmoles/day*	*mEq/day*	*g/day*	*mEq/day*			*g/day*	*mm Hg*		*mEq/L*			*mEq/L*
Control period	1	17.5	47	91	40	8.4	435	5.71	0	24	4	15	39	14	16	18	6.9	6	1	2	0.6	30	7.40	18.1	142	110	3.7
	2	17.0	47	91	40	8.4	1010	5.62	1	96	37	49	59	22	24	28	10.6	6	1	2	0.6	33	7.37	18.2	142	110	3.5
	3		47	91	40	8.4	980	5.72	1	108	52	56	51	22	27	29	10.4	6	1	2	0.6						
	4	17.0	47	91	40	8.4	905	6.21	2	90	45	43	39	12	18	19	8.3	6	1	2	0.6	36	7.36	19.7	142	111	3.8
Period I DCA 8.5 mg/day	5	17.0	87	4	0	8.4	740	6.71	10	9	29	21	14	8	21	18	6.4	3	1	1	0.4						
	6	17.5	87	4	0	8.4	575	7.27	27	3	47	10	6	1	14	19	5.7	3	1	1	0.4	42	7.40	25.1	147	108	3.1
	7		87	4	0	8.4	1000	7.21	39	12	91	29	16	3	34	34	9.6	3	1	1	0.4						
	8	17.0	87	4	0	8.4	570	7.14	23	5	55	9	8	2	14	18	5.6	3	1	1	0.4	39	7.44	25.8	146	106	2.5
	9		87	4	0	8.4	640	7.31	27	3	52	10	8	1	12	19	5.9	3	1	1	0.4						
	10	17.0	87	4	0	8.4	685	7.12	28	4	67	16	16	4	23	30	7.9	3	1	1	0.4	47	7.40	28.2	146	104	2.5
	11		87	4	0	8.4	720	7.26	49	5	88	19	22	2	23	41	8.9	3	1	1	0.4						
	12	16.5	87	4	0	8.4	270	7.81	36	4	62	9	3	0	9	15	4.3	3	1	1	0.4	42	7.41	25.6	146	107	2.1
	13		87	4	0	8.4	575	7.28	27	10	75	9	29	2	23	31	8.1	3	1	1	0.4						
	14	16.5	87	4	0	8.4	475	7.03	14	5	31	9	10	3	10	19	5.1	3	1	1	0.4	42	7.47	29.8	148	102	2.1
	15		87	4	0	8.4	770	7.08	43	7	93	14	31	7	28	38	8.8	3	1	1	0.4						
	16	16.5	87	4	0	8.4	375	7.18	14	9	30	8	9	2	7	19	4.4	3	1	1	0.4	43	7.53	34.6	146	97	2.1
	17	16.5	87	4	0	8.4	760	7.17	34	7	55	22	16	4	21	30	8.8	3	1	1	0.4	44	7.49	32.8	145	96	2.1
	18	16.5	87	4	0	8.4	275	7.35	15	2	34	18	14	1	13	24	6.0	3	1	1	0.4	44	7.49	32.8	144	95	1.7
	19		83	4	0	7.8	635	7.00	18	2	37	17	34	5	17	34	10.2	3	1	1	0.4						
	20	16.5	83	4	0	8.1	650	7.09	19	2	45	18	29	4	18	39	10.5	3	1	1	0.4	50	7.48	36.2	144	93	1.7
Period II	21	16.5	83	4	0	8.2	480	7.23	15	2	51	8	16	2	13	35	9.5	11	1	1	0.7	46	7.48	32.8	143	95	1.8
	22	16.5	84	4	0	8.2	520	7.25	12	5	74	2	15	2	21	40	10.6	11	1	1	0.7	41	7.52	32.5	141	95	1.8
	23		84	4	0	8.4	675	7.12	12	6	71	0	14	4	18	38	10.7	11	1	1	0.7	47	7.45	31.4	140	94	1.8
	24	15.5	86	4	0	8.5	1150	6.90	28	13	126	1	18	10	27	49	15.3	11	1	1	0.7				141	96	1.7
	25	15.5	85	4	0	8.4	490	7.26	14	6	79	0	9	2	18	34	10.1	11	1	1	0.7	42	7.52	32.9	140	94	1.8
	26	15.5	84	4	0	8.2	840	7.08	17	7	98	3	21	6	27	42	15.9	11	1	1	0.7	43	7.51	32.9	139	93	2.2
Period III	27	15.0	4	4	80	8.3	720	7.02	19	3	68	7	13	5	20	27	10.1	5	1	4	0.6	40	7.51	31.3	138	95	2.6
	28	14.5	4	4	80	8.4	760	7.15	28	2	60	36	19	5	25	34	12.8	5	1	4	0.6	41	7.46	28.4	140	98	3.2
	29	14.5	4	4	80	8.3	485	7.19	22	2	25	63	18	4	25	36	11.8	5	1	4	0.6	42	7.47	29.3	134	97	3.6
	30	14.5	4	4	81	8.5	820	6.84	19	2	5	66	26	8	23	33	12.1	5	1	4	0.6						
	31	14.0	4	4	81	8.5	680	6.81	14	2	4	75	20	10	26	29	11.3	5	1	4	0.6	38	7.50	29.0	139	100	3.8
	32	14.5	4	4	80	8.4	460	6.80	13	1	1	45	15	6	14	18	7.5	5	1	4	0.6	36	7.53	29.5	136	98	3.6
Period IV	33	14.5	46	46	81	8.6	710	6.84	25	2	2	91	23	10	28	34	11.6	3	1	2	0.3	37	7.47	26.3	140	101	3.8
	34	14.5	45	45	80	8.7	545	7.10	20	1	3	59	10	3	14	20	6.7	3	1	2	0.3	35	7.50	26.1	143	105	3.8
	35	15.0	45	45	80	8.6	610	6.89	29	2	11	86	15	8	21	32	9.3	3	1	2	0.3	34	7.46	23.1	147	108	4.6
	36	15.0	45	45	80	8.6	620	7.45	39	2	22	64	5	0	14	17	6.3	3	1	2	0.3	36	7.37	19.9	146	114	4.6
	37	15.0	45	45	80	8.4	560	7.59	44	11	38	71	7	0	13	24	6.4	3	1	2	0.3	29	7.37	16.0	145	116	4.7
	38	15.0	45	45	80	8.4	685	6.99	31	47	42	73	11	4	15	19	5.9	3	1	2	0.3	31	7.38	17.9	147	115	4.3
	39		45	45	80	8.4	600	7.30	35	33	27	71	13	1	14	22	6.3	3	1	2	0.3						
	40	15.0	45	45	80	8.4	585	7.14	18	34	39	45	4	1	4	10	4.1	3	1	2	0.3	32	7.38	18.3	144	117	4.4
	41	15.0	45	45	80	8.4	680	7.04	33	46	43	78	11	3	14	24	7.0	3	1	2	0.3	33		18.8	143	116	4.2
	42	15.0	4	4	80	8.4	905	7.02	24	34	24	78	11	2	12	20	6.7	3	1	2	0.3	34	7.35	18.3	146	116	4.1
	43	15.0	4	4	80	8.4	715	7.12	25	5	2	69	6	2	14	22	6.5	3	1	2	0.3						
	44	15.0	4	4	80	8.4	715	7.26	29	4	2	69	5	1	11	19	6.0	3	1	2	0.3	35	7.34	18.5	144	116	4.2

* T.A. = titratable acid.

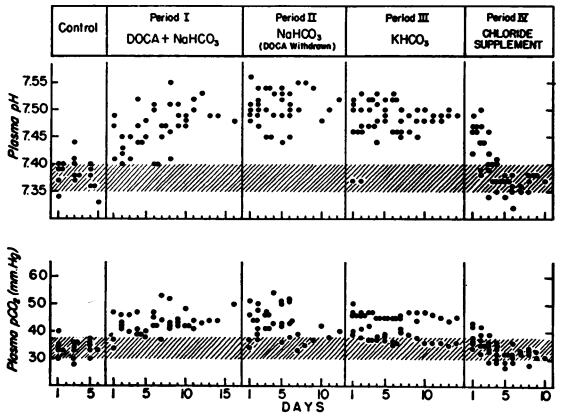

FIG. 4. COLLECTIVE DATA FOR PLASMA pH AND pCO_2 DURING DEVELOPMENT AND CORRECTION OF ALKALOSIS ASSOCIATED WITH POTASSIUM DEFICIENCY.

urine during Period I are difficult to interpret, since no alkali was given during the control period. However, alkali excretion was, in each instance, less than would have been anticipated from a consideration of the average net acid excretion during the control period and the alkali load given during the DCA period (assuming constant endogenous acid production).

Chloride, potassium, and sodium. Plasma chloride concentration fell by an amount that was virtually equal to the rise in plasma bicarbonate concentration (Figures 1–3). Mean plasma chloride concentration initially was 114 mEq per L (range, 111 to 115 mEq per L) and at the end was 96 mEq per L (range, 92 to 99 mEq per L), an average fall of 18 mEq per L. All animals except one (Figure 2) were in persistently negative chloride balance throughout the period. The daily chloride balance expressed cumulatively is shown for three individual experiments in Figures 1–3 and the cumulative values for all animals are shown in Table II.

The plasma potassium concentration fell from a mean control value of 3.9 mEq per L to a mean value of 1.9 mEq per L (range, 1.5 to 2.4 mEq per L) (Figure 5). Most of this reduction in serum concentration occurred in the first 3 or 4 days of the period, as illustrated in Figures 1–3. Cumulative potassium loss ranged from 183 to 265 mEq (Table II); these values were little changed by correction for changes in nitrogen balance (Table II). The daily balance of potas-

TABLE II

Changes in electrolyte balance *

	Dog	Days	Weight		External balance					Internal balance		
			Initial	Final	Cl	Na	K	K corr. for N	N	Intracellular Na	Intracellular K	Δ ECF vol.
			kg	*kg*	*mEq*	*mEq*	*mEq*	*mEq*†	*g*	*mEq*	*mEq*	*L*
Period I												
	S	11	18.5	18.0	−81	+256	−207	−194	−4.8	+281	−188	−0.2
	T	16	17.0	16.5	−59	+418	−254	−284	+10.9	+396	−277	+0.1
	U	11	19.0	18.5	−51	+345	−265	−233	−11.5	+318	−226	+0.1
	W‡	10	17.5	15.5	−153	+67	−225	−228	+0.9	+185	−219	−0.8
	Y	8	18.0	18.0	−38	+356	−183	−204	+7.7	+280	−196	+0.4
Period II												
	S	7	18.0	17.5	−27	−27	−8	−17	+3.2	+20	−19	−0.2
	T	6	16.5	15.5	−33	−77	−20	+51	−26.4	−10	+50	−0.4
	U	13	18.5	17.5	−76	−65	−22	+34	−20.0	+14	+33	−0.5
	W§	6	15.5	15.5	+1	+162	−47	−13	−12.5	+110	−15	+0.6
	Y	6	18.0	17.5	−27	+39	−21	−21	+0.1	+61	−23	−0.1
Period III												
	S	6	17.5	17.5	+7	−192	+182	+187	−1.7	−170	+184	−0.1
	T	6	15.5	14.5	−4	−184	+166	+217	−18.8	−148	+213	−0.2
	U	14	17.5	17.0	−4	−189	+160	+185	−9.9	−141	+182	−0.3
	W	14	15.5	15.0	+15	−242	+170	+176	−2.2	−201	+173	−0.3
	Y	7	17.5	16.5	0	−197	+155	+179	−8.7	−143	+174	−0.2
Period IV												
	S	8	17.5	17.5	+127	+55	+14	−7	+7.7	−74	−11	+0.8
	T	9	14.5	15.0	+203	+128	+65	+37	+10.2	−53	+31	+1.1
	U	10	17.0	17.0	+120	+8	+107	+66	+15.6	−76	+60	+0.6
	W	8	15.0	15.0	+124	−2	+100	+63	+13.4	−74	+54	+0.4
	Y	5	16.5	17.0	+131	0	+81	+64	+6.1	−65	+58	+0.4

* The cumulative balances refer only to the changes which occurred during the individual period.
† 2.7 mEq K/g of N.
‡ Vomited during last 3 days of period.
§ Vomited during first 3 days of period.

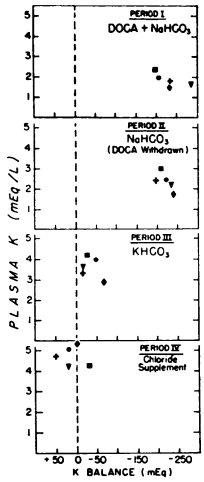

FIG. 5. COLLECTIVE DATA DESCRIBING RELATIONSHIP BETWEEN PLASMA POTASSIUM CONCENTRATION AND CUMULATIVE POTASSIUM BALANCE AT END OF EACH PERIOD. The values for potassium balance have been corrected for changes in nitrogen balance (2.7 mEq per g of nitrogen).

sium (corrected for nitrogen) expressed cumulatively is shown for each dog in Figure 6. (The dog shown for a period of only 7 days, Dog W, vomited on Days 8 through 10.) The data demonstrate that the daily balance of potassium was persistently negative over the entire period of DCA administration, although excretion did diminish as the period progressed.

The upper half of Figure 6 shows the daily sodium balance, expressed cumulatively. The retention of sodium was generally greatest on the first day of steroid administration but despite day-to-day variations in excretion, the pattern throughout the period was one of increasing sodium retention. The cumulative values for the entire period are shown in Table II. Plasma sodium concentration rose by 3 to 4 mEq in nearly every instance. Table II and Figure 6 also demonstrate that in four out of five animals there was a significantly greater retention of sodium than there was loss of potassium. There was no significant weight change (Table II).

Internal balances. Table II shows that the loss of potassium from cells was accompanied by a calculated shift of sodium into cells, ranging from 200 to 400 mEq. In all but one instance (Dog W, which vomited) the uptake of sodium appeared to exceed the loss of potassium. It is also evident from Table II that the estimated cellular uptake of sodium was almost identical to the value for positive external balance of sodium. Calculated extracellular fluid volume did not change significantly.

Organic acids, phosphate, nitrogen, and creatinine. There was no consistent change in organic acid or phosphate excretion (Table I). Values for nitrogen balance were unremarkable (Table II). Plasma creatinine concentration showed no significant change from control values.

Period II: DCA withdrawal

Acid-base. In five dogs there was a slight fall in plasma bicarbonate concentration which averaged 2.1 mEq per L and ranged from 0.8 to 3.9 mEq per L (Figures 1, 2, 3 and 7). In the sixth dog (Dog W, the animal which had vomited during the DCA period and which continued to vomit during the first 3 days after DCA was withdrawn) plasma bicarbonate rose by 6.6 mEq per L. Plasma pH and pCO_2 did not change significantly (Figure 4). There were no striking changes in bicarbonate excretion except in the one animal which showed the largest fall in plasma concentration on the first day of DCA withdrawal (Dog S); this animal simultaneously had a significant

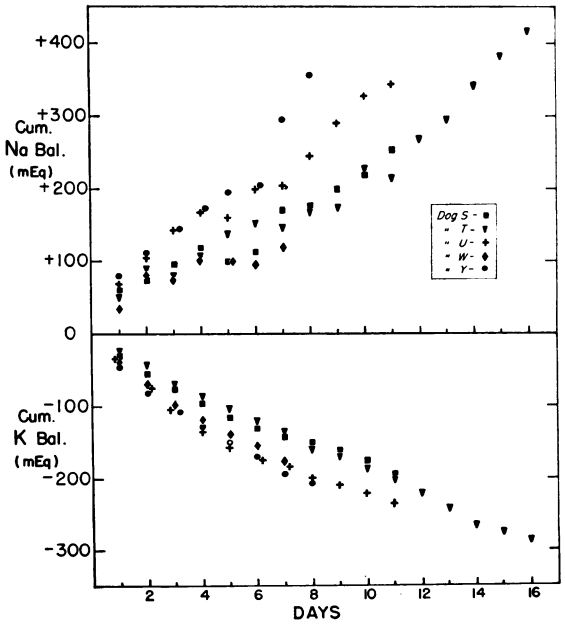

FIG. 6. COLLECTIVE DATA FOR CUMULATIVE BALANCES OF SODIUM AND POTASSIUM DURING ADMINISTRATION OF DCA AND SODIUM BICARBONATE (PERIOD I). The values for potassium balance have been corrected for changes in nitrogen balance (2.7 mEq per g of nitrogen).

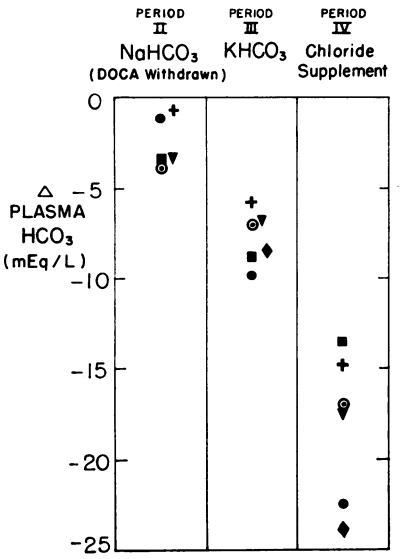

FIG. 7. CUMULATIVE DECREMENTS IN PLASMA BICARBONATE CONCENTRATION DURING RECOVERY FROM METABOLIC ALKALOSIS. Each decrement is calculated as the cumulative reduction from the plasma bicarbonate concentration achieved at the end of the period of DCA and sodium bicarbonate administration (Period I). The total fall, shown at the end of Period IV, had returned the plasma bicarbonate concentration of each dog to the control range of 17 to 20 mEq per L. [Values for Dog W are shown only for Periods III and IV and are calculated as the change from the plasma level at the end of Period II (for explanation see Results).]

increase in bicarbonate output. Several of the other animals showed a moderate reduction in ammonia excretion with the result that net alkali excretion tended to be higher than in the previous period.

Chloride, potassium, and sodium. Plasma chloride concentration remained essentially unchanged in three animals and fell slightly (5 mEq per L) in two. (A fall in chloride concentration of 17 mEq per L occurred in Dog W, which vomited during the first 3 days of the period.) Small quantities of chloride continued to appear in the urine following DCA withdrawal with the result that there was a further small cumulative negative balance (Table II).

Plasma potassium tended to rise slightly (Figure 5). Within 2 days after DCA withdrawal, potassium excretion fell to negligible levels (Table I). There was usually a slight fall in plasma sodium concentration which averaged 4 mEq per L. Sodium retention, which had been a prominent feature of the DCA period, promptly ceased, except in Dog W, which retained sodium after vomiting stopped. In two animals (Figures 1 and 2) there was a small loss of sodium, but even in these, cumulative sodium balance was still markedly positive at the end of the period (Dog T, 341 mEq; Dog U, 280 mEq).

Internal balance. Calculated shifts of sodium and potassium were minor (Table II), except in Dog W, which showed a significant gain of intracellular sodium.

Organic acids, phosphate, nitrogen, and creatinine. Organic acid and phosphate excretion did not change significantly nor did plasma creatinine concentration. There was a significant negative nitrogen balance in two dogs (Table II).

Period III: Replacement of sodium bicarbonate by potassium bicarbonate

Acid-base. Figures 1–3 illustrate that there was a moderate fall in plasma bicarbonate concentration during the period of potassium bicarbonate administration, and they also show that virtually all of this fall occurred during the first 1 or 2 days of the period. The reduction in plasma level for the entire period is shown for each animal in Figure 7. The average fall for the group was 5.7 mEq per L; the final average plasma value of 29.0 mEq per L was 10 mEq above the mean value observed at the end of the control period. In two animals plasma pH and pCO_2 fell slightly; in the remainder there was no significant change (Figure 4).

A marked increase in net alkali excretion occurred on the first day of the period in the two dogs which simultaneously showed the largest reductions in plasma bicarbonate concentration. There were no other consistent changes in the acid-base composition of the urine.

Two dogs (as mentioned under Methods) received an additional quantity of 1.5 mmoles per kg of potassium bicarbonate on 4 successive days near the end of the period. The observations on one such dog are illustrated in Figure 2, in which it can be seen that plasma bicarbonate fell by 2.5 mEq per L during the period of extra potassium bicarbonate administration and that it rose by approximately 1 mEq per L after the potassium supplement was stopped. In the other animal

there was no significant change in plasma bicarbonate concentration either during or after the administration of extra potassium bicarbonate.

Chloride, potassium, and sodium. The plasma chloride concentration rose by an average of 7 mEq per L (range, 4 to 12 mEq per L). This rise usually occurred gradually (Figures 1 and 2), but occurred more abruptly in the two animals which had a marked bicarbonate diuresis on the first day. The mean plasma chloride concentration at the end of the period was 98 mEq per L, a value of 16 mEq per L below control levels. There was no significant positive or negative chloride balance during this period of observation (Table II).

The addition of potassium bicarbonate to the diet resulted in a marked retention of potassium with the restoration of more than half of the deficit within the first 2 days. During the next 2 to 3 days a smaller additional quantity of potassium was retained with the result that an average of 85 per cent of the estimated initial losses (expressed as potassium corrected for nitrogen) was replaced (Table II). Subsequently, potassium excretion became virtually equal to potassium intake. The pattern of potassium retention for three individual experiments is shown in Figures 1–3, and the cumulative balance of potassium from the beginning of the study is shown in Figure 5. This latter figure also demonstrates that serum potassium concentration rose from a mean level of 2.3 to 3.6 mEq per L (range, 2.9 to 4.2 mEq per L) during the period.

Each of the two dogs given an extra supplement of potassium bicarbonate (Dogs U and W) retained 20 mEq of potassium over the 4-day loading period.

During the first several days of the period there was a large negative balance of sodium (as illustrated in Figures 1–3), but within 6 to 7 days urinary excretion of sodium had virtually ceased. The cumulative negative sodium balance for the period (Table II) ranged from 184 to 242 mEq. There was no significant weight loss, nor was there any consistent change in plasma sodium concentration.

Internal balances. Table II indicates that cellular accumulation of potassium was accompanied by an almost equal loss of sodium. Furthermore, the calculated shift of sodium from cells was approximately equal to the negative external sodium balance for the period (Table II). Calculated extracellular fluid volume fell slightly.

Organic acids, phosphate, nitrogen, and creatinine. Organic acid excretion showed no consistent or significant change, nor was there any change in phosphate excretion. Nitrogen balance was slightly negative in most dogs (Table II). Plasma creatinine concentration did not change significantly.

Period IV: Administration of chloride

Acid-base. The addition of chloride to the diet resulted in a fall in plasma bicarbonate concentration varying from 6.7 to 16.4 mEq per L over a period of 3 to 5 days. Figures 1–3 illustrate that when chloride was given with sodium or potassium, or was substituted for phosphate, the effect on plasma bicarbonate concentration was the same. The fall in concentration at the end of the period averaged 10.4 mEq (Figure 7), representing approximately two-thirds of the decrement in plasma concentration seen during the entire course of the study. Final plasma concentrations ranged between 17.4 and 19.6 mEq per L. Blood pH fell abruptly to control levels, and there was a slight but consistent fall in pCO_2 (Figure 4) which returned all values to the normal range. In four experiments, after a steady state had been achieved, the chloride supplement was discontinued and the

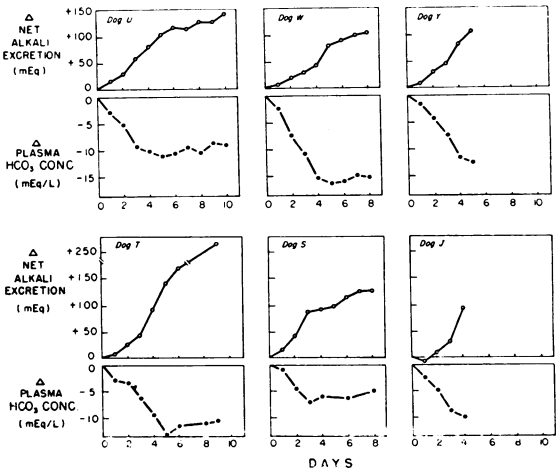

FIG. 8. CUMULATIVE DECREMENTS IN PLASMA BICARBONATE CONCENTRATION AND INCREMENTS IN NET ALKALI EXCRETION DURING THE PERIOD OF CHLORIDE ADMINISTRATION (PERIOD IV).

animals were maintained on only potassium bicarbonate. The withdrawal of chloride did not cause any further significant alteration in the plasma bicarbonate concentration (Figures 1 and 2).

Figure 8 shows that during the interval when plasma bicarbonate concentration fell, there was an increase in net alkali excretion in every animal. Cumulative change in net alkali excretion for the period (calculated as the change from the average net alkali excretion during the 3 days before the start of the period) ranged between 92 and 266 mEq.

Chloride, potassium, and sodium. All animals retained chloride for a period of 4 to 5 days; cumulative values are shown in Table II (and Figures 1–3). In the two dogs given sodium chloride, the ratio of chloride to sodium retained was greater than would be required simply for expansion of extracellular fluid with a normal chloride-sodium ratio; the values for "excess chloride" were 85 and 105 mEq. The cumulative values for chloride retention in the dogs whose deficits were repaired during the administration of a sodium-free diet ranged from 120 to 131 mEq. Plasma chloride concentration rose to a level of 112 to 116 mEq per L. The average rise was 16 mEq per L, an increment 5 mEq greater than the simultaneous average decrement in plasma bicarbonate concentration.

Plasma potassium concentration rose in every animal; the average increase was 1.0 mEq per L and the final values ranged from 4.2 to 5.3 mEq per L (Figure 5). During this final period there was significant retention of potassium in all but one animal (Table II). However, over the first 3 to 5 days, during which plasma bicarbonate concentration fell to normal, there was no significant retention of potassium (− 5 and + 17 mEq, corrected for nitrogen) in the two dogs given a sodium chloride supplement; in the other three animals potassium retention over this interval ranged from 47 to 64 mEq.

There was no significant change in plasma sodium concentration. Sodium balance was unchanged in the three animals on a low sodium intake but was positive (+ 55 and + 128 mEq) in the two dogs given a sodium chloride supplement. All animals, except the one which had vomited during Periods I and II (Dog W), were still in positive sodium balance at the end of the study (as illustrated in Figures 1–3) in amounts ranging from 92 to 285 mEq.

Internal balances. Internal balance calculations indicated that there was a small shift of sodium out of cells and of potassium into cells. The calculated extracellular fluid volume increased slightly in every animal (Table II).

Organic acids, phosphate, nitrogen, and creatinine. The excretion of organic acids and phosphate did not change significantly. Nitrogen balance was positive in every case and cumulative nitrogen retention averaged 11 g (Table II). There was no significant variation in the plasma creatinine concentration.

Fecal electrolytes. During the control period, Period I, and Period II, stool potassium averaged 1 to 2 mEq per day. During Periods III and IV (the interval over which potassium was administered), stool potassium rose to an average of 4 mEq per day. Stool sodium during the control, first, and second periods averaged 5 to 8 mEq per day. During Periods III and IV, stool sodium fell to an average of 1 to 2 mEq per day. Stool chloride was approximately 1 mEq per day throughout the study.

DISCUSSION

The present data indicate that chloride plays a critical role in permitting full correction of the alkalosis associated with potassium depletion in dogs. Although plasma bicarbonate concentration rose by an average of 17 mEq per L during the period of DCA administration and potassium depletion, it fell by an average of only 7 mEq per L when DCA was withdrawn and the potassium deficit was almost entirely corrected by administration of potassium bicarbonate. The largest fall in plasma bicarbonate concentration, as well as in plasma pH, occurred when chloride was subsequently added to the diet; the provision of chloride (either as sodium chloride or potassium chloride, or by substitution of chloride for phosphate) produced an average fall of 10 mEq per L in plasma bicarbonate concentration and restored acid-base equilibrium to normal. The marked retention of chloride during this period was accompanied by an increase in net alkali excretion which, assuming constant endogenous acid production, was of sufficient magnitude to

wholly account for the fall in plasma bicarbonate concentration. It should be emphasized, however, that it is not necessary to rely on the assumption that endogenous acid production was unchanged during the interval of chloride administration in order to reach the conclusion that the kidney was ultimately responsible for correction of the alkalosis. Continued excretion of a substantial quantity of bicarbonate, at a time when the plasma level was falling, clearly indicates that the bicarbonate reabsorptive capacity of the kidney had been appreciably reduced.

It is apparent that the addition of chloride to the diet, of necessity, always involved a change in the intake of some other ion. However, the use of three separate maneuvers for chloride repletion would appear to make it unlikely that there was any factor other than the augmented chloride intake which was responsible for the corrective process. The presence of sodium in the diet was shown to be unnecessary in the studies with potassium chloride supplements; the effect of potassium loading was controlled by the preliminary administration of an equimolar quantity of potassium bicarbonate; the substitution of chloride for phosphate permitted correction without change in the cation content of the diet.

It is not possible to decide from the present data whether the potassium retention which usually, but not always, occurred during the period of chloride administration played a role in the correction of the alkalosis or simply occurred as a consequence of the restoration of normal acid-base equilibrium. However, several observations suggest that the latter interpretation is the more likely one. It is known, for example, that metabolic alkalosis produced by peritoneal dialysis with sodium bicarbonate, in itself, produces potassium depletion (9). Furthermore, the degree of potassium depletion induced by this type of alkalosis is comparable to that which persisted in the present study after potassium bicarbonate had been administered for a prolonged period. However, even if it is argued that the small but persistent deficit was responsible for the maintenance of the alkalosis, it is clear that only with repair of the chloride deficit could the additional potassium be retained; thus chloride would, in any event, have to be considered the primary element in the corrective process.

Although the data allow no firm conclusion concerning the intimate mechanism by which chloride operates to modify the renal handling of bicarbonate, it seems most likely that its role is fundamentally the same as has been previously proposed for the recovery phase of chronic respiratory acidosis (1). In these latter studies it was shown that, despite restoration of a normal plasma carbon dioxide tension, the plasma bicarbonate concentration remained significantly elevated and plasma chloride concentration grossly subnormal, when a diet deficient in chloride was administered. It was tentatively proposed that when the quantity of chloride available for reabsorption is insufficient to reduce the potential difference generated by active sodium transport, accelerated diffusion of hydrogen into the tubular lumen continues and sustains plasma bicarbonate concentration at an elevated level. The present observations are consistent with this general hypothesis concerning the role of chloride and also with earlier studies indicating that the rate of acid excretion can be markedly increased in the nonacidotic dog when the availability of a penetrating anion such as chloride is severely limited (4). In these latter experiments, the infusion of phosphate induced near-maximal excretion of titratable acid; the subsequent administration of chloride (but not of anions of low penetrating ability such as sulfate or ferrocyanide) was followed by a marked suppression of acid excretion.

The results of the present study differ in several major respects from those of previous investigators. Grollman and Gamble (10) have noted that a mild alkalosis induced by 1 to 6 days of DCA administration and a potassium-free diet was fully corrected by the subsequent withdrawal of DCA. The authors concluded that the increase in bicarbonate concentration which occurs with DCA therapy is a direct steroid effect. However, the findings of the present study provide little support for this view; after withdrawal of DCA, plasma bicarbonate concentration fell by an average of only 2 mEq per L, the plasma level remaining 15 mEq per L above control levels. It is conceivable that some difference in the protocol of Grollman and Gamble (such as the presence of a substantial quantity of chloride in their diet) accounts for the difference in results of the two

studies, but no conclusions can be drawn at the present time.

The response to potassium bicarbonate administration in the present study also differed markedly from that observed by previous workers (11), who noted that this potassium salt fully corrected the alkalosis induced in rats by DCA and a potassium-free diet. Correction occurred in association with only minor changes in the acid-base composition of the urine (the urine remaining acid); most of the fall in plasma bicarbonate concentration apparently resulted from increased organic acid production as manifested by a striking rise in the excretion of organic anions (11). By contrast, as pointed out earlier, in the dog only partial correction of the alkalosis occurred during potassium bicarbonate administration (average fall of 5 mEq per L in plasma bicarbonate concentration) and there was no significant increase in organic anion excretion.

The retention of sodium without chloride induced in the present study by the administration of DCA and sodium bicarbonate apparently led to little, if any, expansion of the extracellular fluid; virtually all the retained sodium (according to "chloride space" calculations) served to replace potassium lost from the cells. These findings stand in contrast to the results of previous studies with DCA (12, 13) in which the diet contained sodium chloride. Under the latter circumstances, most of the sodium was retained with chloride and presumably was restricted to the extracellular space. It has been proposed that the resulting increase in extracellular fluid volume produced a rise in glomerular filtration rate which was responsible for the characteristic "escape" from the sodium-retaining effects of DCA (12, 14). In the absence of such an expansion and of a rise in glomerular filtration rate, the mechanism of "escape" would not be expected to operate; this may account for the persistent sodium retention observed in dogs on a chloride-free intake.

SUMMARY

Balance studies have been carried out on six dogs in order to assess the factors governing correction of the metabolic alkalosis associated with potassium deficiency.

Alkalosis and hypochloremia were induced by the administration of deoxycorticosterone acetate (DCA), sodium bicarbonate, and a diet of low potassium and chloride content; there was an average increase of 17 mEq per L in plasma bicarbonate concentration accompanied by a virtually equal reduction in plasma chloride concentration. Withdrawal of DCA was followed by an average fall of 2 mEq per L in plasma bicarbonate concentration. Administration of potassium bicarbonate in place of sodium bicarbonate produced a further average fall of only 5 mEq per L in plasma bicarbonate concentration despite almost complete repair of the potassium deficit. Thus, mean plasma bicarbonate concentration was still 10 mEq above control levels after equilibrium between potassium intake and excretion had been established. The subsequent administration of chloride as either sodium chloride, potassium chloride, or by substitution of chloride for phosphate was accompanied by a prompt reduction in plasma bicarbonate concentration to control levels. In each dog there was an increase in net alkali excretion as chloride was retained. These data, taken together with previous observations on the recovery from chronic respiratory acidosis, suggest that under a variety of circumstances chloride plays a critical role in permitting an elevated plasma bicarbonate concentration to return to normal levels. A hypothesis which may account for the influence of chloride on the transtubular movement of hydrogen ions into the glomerular filtrate has been considered.

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