WATER AND ELECTROLYTE STUDIES IN CHOLERA *

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Rational treatment of cholera cannot be provided without precise knowledge of the water and electrolyte losses which occur in this disease; such information is not available in the literature. Studies prior to 1900 usually reported electrolyte concentrations in whole blood, not in plasma, and sodium and chloride were frequently reported as NaCl. Since 1900 there have been many reports of electrolyte concentrations in plasma or fecal excreta but only one preliminary report (1) relates fecal losses to plasma levels in the same patient. However, this report suffers, as do all others on cholera, from the fact that oral intake was not restricted and it is not certain to what extent fecal electrolytes had been diluted with oral fluids.

The 1958 cholera epidemic in Bangkok, Thailand, provided the opportunity to perform quantitative, volumetric studies of water and electrolytes in plasma, feces and urine for the first 24 hours after admission in patients suffering from cholera. During this period oral food and fluids were withheld and the dehydration and acidosis were treated by intravenous fluids. The effect of water and sodium loading on electrolyte exchange was also observed and whole blood and plasma analyses were repeated on each patient in convalescence.

MATERIALS

Twenty-five patients with diarrhea were admitted to a study ward provided by the Chulalongkorn University Medical School at the Bangkok Red Cross Society Hospital during June and July, 1958. A positive culture of *Vibrio comma* was obtained on 17 of these patients once or more often. As the 1958 epidemic was confined principally to Bangkok and nearby suburbs, patients were able to reach well-staffed hospitals soon after the onset of their symptoms. The majority of patients were received in fair condition; however, several patients were in moderate shock with systolic blood pressures under 100 mm. Hg. There was one death: an 83 year old woman with electrocardiographic evidence of cardiac disease died three days after admission.

A venous blood sample was obtained on admission; thereafter blood, urine, and feces were collected at intervals of one to four hours during the first 24 hours, then less frequently until the diarrhea ceased. Convalescent blood samples were taken prior to discharge. Five patients left against advice soon after their diarrhea ceased; some of these "convalescent" values may not accurately represent their normal blood composition.

Care was taken to avoid spillage of feces. A large bore rectal tube was used for the first 24 hours in addition to a cholera bed in which the patients' buttocks were placed over an opening in the bed frame and excreta collected in five gallon containers. Retention catheters were placed in the bladder for the first 24 hours to facilitate urine collection. Urine and feces were measured in graduated cylinders to the nearest 5 ml. Aliquots of fecal material were filtered through glass wool and a Seitz filter. Blood samples were heparinized and the plasma separated immediately after a sample for duplicate hematocrits and whole blood specific gravities had been obtained. Fecal specimens and blood for plasma CO_2 content were collected under oil and analyzed within 20 minutes.

During the first 24 hours of observation and treatment, patients were given nothing by mouth with the exception of four who were given carmine dye with 100 ml. of water in order to measure bowel transit time. After 24 hours, fluids were given *ad libitum* and a diet of rice gruel, boiled eggs and milk was allowed. All patients received an antibiotic, either chloramphenicol or a tetracycline derivative, after the 24 hour observation period and had at least one cholera-negative stool culture prior to discharge. Patients 13 and 18 probably had cholera but repeated attempts to culture the *V. comma* were unsuccessful.

* The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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METHODS

The following procedures were performed: whole blood (Gb) and plasma (Gp) specific gravities (2); microhematocrit (Vc) (3); carbon dioxide content of plasma and feces (4); sodium and potassium concentrations of plasma, feces and urine by internal standard flame photometry; and a Fiske osmometer was used for osmolarity determinations of plasma and feces. All determinations were done in duplicate and the results averaged.

The intravenous treatment schedule recommended by Johnson, Weaver and Phillips (5) was followed using the copper sulfate method (2) for determination of Gp. Normal saline was infused rapidly in amounts calculated to correct the initial dehydration (200 ml. for each 0.001 increase in Gp above 1.025). Following this, fluids were given to match measured urine and fecal losses or to correct elevations in Gp. A detailed evaluation and discussion of this method based on the results of the present study will be presented elsewhere (6).

Sodium bicarbonate was infused as a 2 or 4 per cent solution to treat acidosis and potassium was given in small amounts. In order to obtain more information on electrolyte exchange, ideal treatment schedules were not adhered to in all patients. Several of the later patients were given nonelectrolyte (5 per cent dextrose in distilled water) and hypertonic (2 per cent saline) or Roger's solution (1.35 per cent saline) infusions in an attempt to alter fecal electrolyte concentrations. The epidemic subsided before additional planned experiments could be completed.

RESULTS

Table I lists pertinent admission data and 24 hour intake and output volumes for the 17 proven cholera patients. For comparison the table has been divided into two sections: patients having over 3 L. of fecal excretion and patients having under 3 L. during the first 24 hours.

Tables II and III list the results of plasma and whole blood examinations performed at the following times: immediately on admission, following initial rehydration, 24 hours after admission and in convalescence. All plasma electrolytes, CO_2 contents and osmolarity values have been cor-

Table I

Twenty-four hour intake and output and fecal electrolyte concentrations in cholera patients with (A) over 3 liters fecal excreta and (B) under 3 liters

Patient	Sex	Age	Weight Kg	I. V. fluids Volume	Urine Volume	Fecal Volume	Fecal electrolyte contents Na	Cl	K	CO_2	Osmolarity
							mEq/L				mOsm/L
					A						
1	M	28	65	10,200	1,425	3,465	130	68	33.3		337
2	M	83	45	18,100	305	11,430	165	107	9.5		328
3	M	30	43	12,100	1,795	6,750	142	109	15.6		291
5	F	15	36	6,700	1,005	3,125	152	123	13.6		307
6	F	30	35	19,400	210	7,700	135	130	14.8		311
8	M	38	55	13,250	360	8,320	139	107	16.5		324
10	F	23	34	10,700	1,650	5,650	119	104	16.7	46.3	259
12	F	23	40	10,500	1,480	7,260	132	113	14.3		297
14	M	58	58	13,000	855	10,000	129	93	16.0	51.4	279
15	M	34	55	21,000	1,175	17,435	142	118	9.7	42.7	279
21§	M	23	52	12,880	1,665	8,240	122	100	17.3	40.2	282
Mean				13,200	1,085	8,125	137	107	16.1	45.2	300
					B						
7*	F	83	30	9,220	930	2,885	139	121	16.2		288
9	F	46	42	9,600	1,690	2,870	131	105	24.9		273
20§	M	57	37	11,200	2,630	2,700	123	114	27.8	31.7	285
23§	M	22	52	6,000	1,335	880	82	58	40.0	60.5	232
24§	M	23	39	4,700	3,030	1,870	122	78	23.9	45.9	266
25§	F	35	50	3,500	545	2,860	85	60	25.7	35.7	254
Mean				7,370	1,700	2,345	114	89	26.4	43.5	266

* Died

§ Treated with non-electrolyte intravenous solutions as well as with normal saline

TABLE II

Whole blood and plasma values in patients with over 3 liters fecal excreta per 24 hours

Patient	Period	Time	Vc	Gb	Gp	CO_2*	Na*	Cl*	K*	Osmolarity*	Total Protein§
						m Eq / L				mOsm/L	
	Admission		62	1.071	1.040	13.7	168	118	6.5		11.9
	Rehydration	2 hrs.	48	1.058	1.028	14.0	168	127	6.3		7.8
1	24 Hours		38	1.052	1.021	24.0	152	118	3.0	373	5.2
	Convalescence	2 days	38	1.051	1.021	22.1	152	120	3.8		5.2
	Admission		52	1.067	1.042	22.2	162	119	4.5		13.0
	Rehydration	2 hrs.	50	1.065	1.032	18.3	149	116	4.3		9.3
2	24 Hours		31	1.045	1.023	27.6	160	122	2.8	364	5.9
	Convalescence	7 days	35	1.050	1.023	29.3	157	120	3.8	324	5.9
	Admission		55	1.068	1.038	19.4	168		4.8	424	11.2
	Rehydration	1/2 hr.	42	1.051	1.024	18.4	153	119	4.4	345	6.3
3	24 Hours			1.052	1.024	15.2	152	124	4.0	335	6.3
	Convalescence	3 days	39	1.052	1.026	22.8	154	117	3.9		7.0
	Admission		47	1.059	1.033	19.5	151	118	3.8	326	9.6
	Rehydration	1 hr.	33	1.043	1.024	18.0	155	131	3.4	288	6.3
5	24 Hours		33	1.047	1.025	17.0	149	130	3.5	321	6.7
	Convalescence	3 days	35	1.050	1.025	26.5	155	121	3.3	314	6.7
	Admission		44	1.060	1.038	15.0	149	111	3.5	337	11.2
	Rehydration	2 hrs.	29	1.044	1.026	16.3	152	126	3.1	323	7.0
6	24 Hours		25	1.043	1.025	14.9	162	146	2.8	350	6.7
	Convalescence	4 days	25	1.040	1.022	28.0	149	112	2.2	296	5.5
	Admission		61	1.073	1.043	22.1	158	113	5.2		13.4
	Rehydration	1-1/2 hr.	44	1.055	1.030	21.1	150	124	4.6	336	8.5
8	24 Hours		41	1.052	1.027	23.1	159	124	3.9	359	7.4
	Convalescence	4 days	41	1.053	1.028	27.4	142	108	3.3	301	7.8
	Admission		57	1.068	1.041	14.0	157	129	4.8	364	12.7
	Rehydration	1 hr.	39	1.050	1.025	17.0	156	137	6.8	347	6.7
10	24 Hours		31	1.047	1.024	23.1	166	131	3.3	327	6.3
	Convalescence	6 days	32	1.047	1.025	37.0	153	112	3.3	341	6.7
	Admission		50	1.064	1.041	11.1	155	129	4.3	377	12.7
	Rehydration	1-1/2 hr.	41	1.054	1.031	15.4	155	135	6.2	380	8.9
12	24 Hours		29	1.046	1.025	18.5	169	139	2.9	353	6.7
	Convalescence	3 days	32	1.048	1.025	30.4	161	116	3.1	295	6.7
	Admission		51	1.060	1.032	22.7	149	118	4.5	337	9.3
	Rehydration	1 hr.	42	1.054	1.029	22.1	148	124	4.9	367	8.1
14	24 Hours		41	1.053	1.026	23.9	152	120	3.1	321	7.0
	Convalescence	6 days	36	1.052	1.026	28.1	148	112	3.3	334	7.0
	Admission		62	1.072	1.039	20.5	155	117	4.9		11.5
	Rehydration	1/2 hr.	52	1.059	1.029	23.0	147	124	6.4	391	8.1
15	24 Hours		38	1.054	1.026	40.3	177	128	2.8	373	7.0
	Convalescence	7 days	43	1.052	1.023	33.3	152	110	3.4		5.9
	Admission		59	1.070	1.040	19.2	155	116	5.9		12.3
	Rehydration	2 hrs.	48	1.058	1.029	19.4	145	119	6.3	338	8.1
21	24 Hours		37	1.051	1.025	25.9	156	125	3.6	332	6.7
	Convalescence	2 days	42	1.053	1.028	22.8	147	119	4.0	316	7.8
	Mean Values										
	Admission		54.4	1.067	1.039	18.1	158	119	4.8	361	11.7
	Rehydration		42.6	1.054	1.028	18.5	153	126	5.2	346	7.7
	24 Hours		34.4	1.049	1.025	23.0	159	128	3.2	346	6.5
	Convalescence		36.2	1.050	1.025	28.0	151	115	3.4	315	6.6
	Normal Ranges		40-44	1.056-1.058	1.025-1.027	25.7-30.0	146-156	107-114	3.8-5.4	300-322	7.2-7.8

Vc = hematocrit; Gb = blood specific gravity; Gp = plasma specific gravity.
* Converted to mEq or mOsm per liter plasma water (see text)
§ Derived from Gp (8).

rected for plasma protein concentrations by conversion to mEq. or mOsm. per L. of plasma water using Eisenman, MacKenzie and Peters' formula (7) Wp = 98.4 − (0.718Pp) where Wp = plasma water and Pp = plasma protein concentration.

On admission the extent of dehydration is evident from the elevation of Gp and of plasma osmolarity. Vc and Gb are higher than convalescent values but in several instances (Patients 6, 7 and 25) they are in the range of normal due to severe

TABLE III

Whole blood and plasma values in patients with under 3 liters fecal excreta per 24 hours

Patient	Period	Time	Vc	Gb	Gp	CO_2*	Na*	Cl*	K*	Osmolarity*	Total Protein§
							m Eq / L			mOsm/L	
	Admission		40	1.057	1.029	19.7	151	113	4.6	339	8.1
	Rehydration	2 hrs.	30	1.048	1.028	18.3	150	121	4.0	349	7.8
7	24 Hours		31	1.049	1.025	17.4	151	126	3.6	360	6.7
	Convalescence	(Died)									
	Admission		54	1.064	1.034	21.5	152	122	5.2	343	10.0
	Rehydration	2-1/2 hrs.	41	1.055	1.025	17.6	153	137	5.1		6.7
9	24 Hours		39	1.049	1.023		156	139	3.2	338	5.9
	Convalescence	4 days	37	1.050	1.022	23.8	150	116	3.3	303	5.5
	Admission		57	1.064	1.034	17.0	151	121	7.5	337	10.0
	Rehydration	3 hrs.	47	1.058	1.027	15.6	154	128	5.8	329	7.4
20	24 Hours		36	1.047	1.023	22.6	153	126	5.7	325	5.9
	Convalescence	2 days	38	1.049	1.023	35.5	145	119	4.2	323	5.9
	Admission		53	1.065	1.035	19.8	167	117	5.4		10.4
	Rehydration	1 hr.	47	1.058	1.030	21.1	137	108	4.0	347	8.5
23+	24 Hours		37	1.049	1.025	31.7	154	115	3.8	322	6.7
	Convalescence	2 days	38	1.051	1.026	28.2	151	116	3.5	322	7.0
	Admission		53	1.062	1.032	23.4	148	112	2.8		9.3
	Rehydration	1 hr.	46	1.054	1.026	22.9	139	104	3.2		7.0
24+	24 Hours		42	1.052	1.026	24.1	143	118	3.9	323	7.0
	Convalescence	4 days	41	1.049	1.024		136	116	3.5	290	6.3
	Admission		41	1.059	1.034	13.2	151	124	4.2	327	10.0
	Rehydration	2 hrs.	30	1.048	1.027	21.5	154	127	3.4	319	7.4
25	24 Hours		28	1.046	1.025	19.3	147	122	3.2		6.7
	Convalescence	2 days	29	1.048	1.028	20.0	148	121	3.5	316	7.8
	Mean Values										
	Admission		49.7	1.062	1.033	19.1	153	118	5.0	337	9.6
	Rehydration		40.2	1.054	1.027	19.5	148	121	4.3	336	7.5
	24 Hours		35.5	1.049	1.025	23.0	151	124	3.9	334	6.5
	Convalescence		36.6	1.049	1.025	26.9	146	118	3.6	311	6.5
	Normal Ranges		40-44	1.056-1.058	1.025-1.027	25.7-30.0	146-156	107-114	3.8-5.4	300-322	7.2-7.8

Vc = hematocrit; Gb = blood specific gravity; Gp = plasma specific gravity.
* Converted to mEq or mOsm per liter plasma water (see text)
§ Derived from Gp (8).
\+ Initially rehydrated with 5 per cent dextrose in distilled water.

anemia. When electrolyte and osmolarity determinations are corrected for the volume occupied by plasma proteins, mean sodium and chloride levels in patients with over 3 L. of fecal excreta are higher than those considered to be normal and are also higher than the patients' own convalescent values. In addition to dehydration, acidosis is evident in all patients.

Following the period of initial rehydration which took from 30 to 180 minutes and involved infusions of 1.5 to 3.6 L. of normal saline, marked improvement in hydration as measured by Gp and osmolarity occurred. There was no appreciable change in plasma CO_2 content as bicarbonate solutions were not given during this period. Elevated chloride values seen on admission persisted during the treatment.

Observations at the end of 24 hours of treatment indicated improvement in CO_2 content and maintenance of fluid balance. It will be noted that in most patients values for plasma sodium and chloride are elevated above values found in convalescence.

Vc and Gb values in convalescence revealed severe anemia in several patients. Hypoproteinemia was apparent in several patients but was not as severe nor as frequent as anemia. These low values were probably due to the poor nutritional state and to parasitic infections of the socio-economic class who were cholera victims. A mild alkalosis persisting into convalescence was observed in Patients 10, 12, 15 and 20.

Table I lists individual volumes, electrolyte concentrations, osmolarities and their mean values in

TABLE IV

Fecal volumes and electrolyte concentrations during the first 24 hours in patients with non-cholera diarrhea

Patient	Volume	Na	Cl	K	CO_2	Osmolarity
		mEq/L				mOsm/L
11	480	45.1	41.8	29.4		310
18	870	71.0	29.0	29.1	47.0	300
22	290	113.0	59.6	10.7	48.9	297
Mean	545	76.4	43.5	23.0	47.9	302

the feces of cholera patients. Of interest are the high concentrations of potassium and carbon dioxide in the excreta. Data are available (Table IV) on fecal electrolyte concentrations in three patients with diarrhea not caused by cholera. Other non-cholera patients did not have sufficient watery stools during the observation period.

Figure 1 relates plasma and fecal concentrations of sodium and intravenous intake and fecal output volumes during treatment. A close correlation between plasma and fecal sodium levels is apparent. The patient, an 83 year old man, was treated cautiously as his renal function and cardiac reserve were unknown. Acidosis was effectively

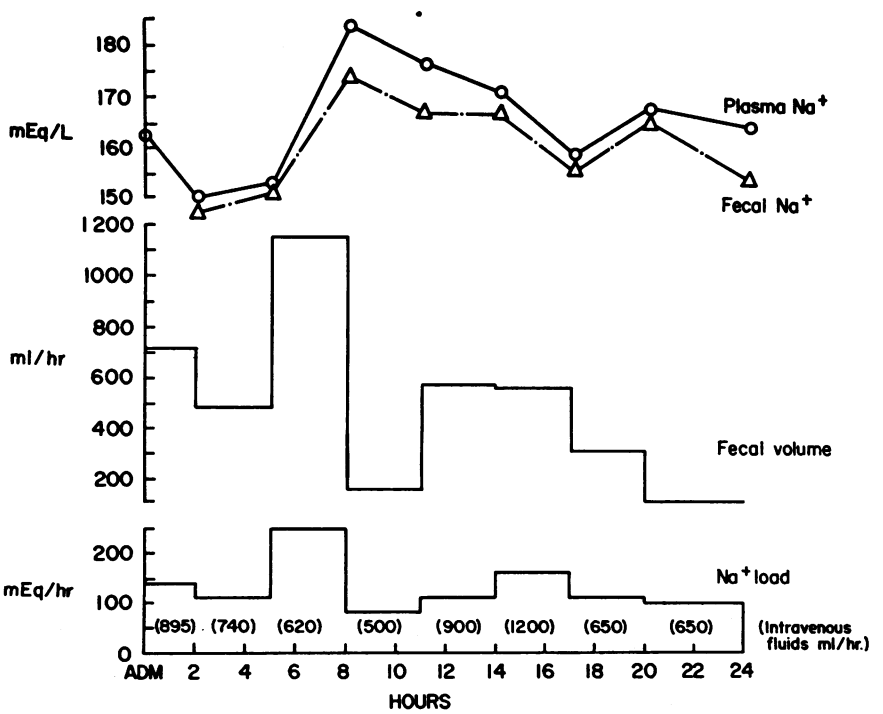

FIG. 1. PATIENT NO. 2. PLASMA AND FECAL SODIUM CONCENTRATIONS, FECAL VOLUME AND VOLUME OF INTRAVENOUS FLUIDS DURING VARYING SODIUM LOADS

Isotonic sodium chloride was infused continuously at different hourly rates. Between hours five and eight, 4 Gm. $NaHCO_3$ per 100 ml. was added to the infusion.

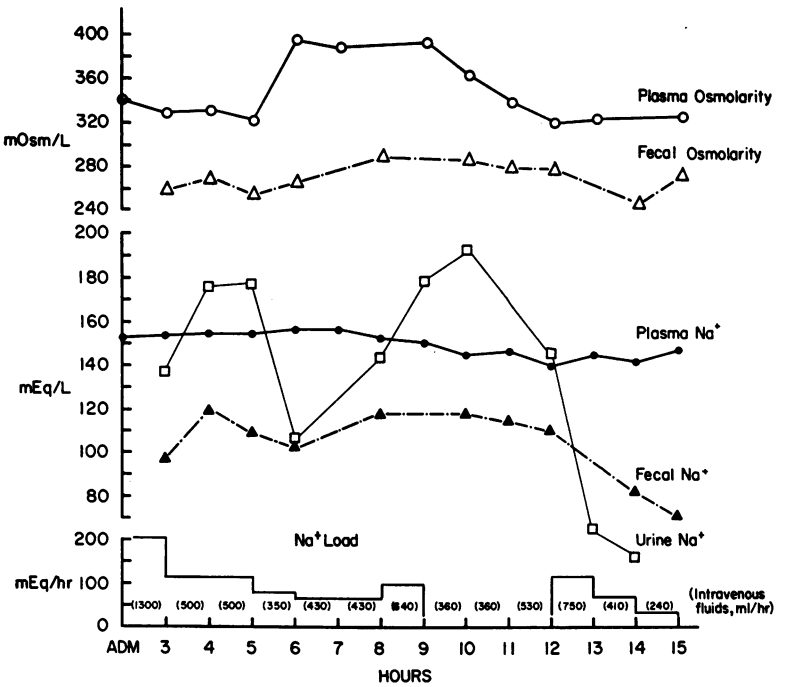

FIG. 2. PATIENT NO. 20; RESPONSE OF PLASMA, FECAL AND URINARY SODIUM AND PLASMA AND FECAL OSMOLARITY TO SODIUM AND WATER LOADING

Between hours 9 and 12, 5 per cent dextrose in water was substituted for normal saline. Following water loading fecal sodium concentration decreases. Proportionate increase in fecal potassium levels (not shown) maintains fecal osmolarity.

corrected but rehydration, based on observed fecal and urine volumes, was inadequate probably because the patient sequestered a large volume of feces in his bowel from a temporary ileus which was released several hours after admission. When this was realized, intravenous fluids were increased and adequate urine output was soon established.

Figures 2 and 3 show changes in plasma, fecal and urine sodium concentrations as well as plasma and fecal osmolarity values in response to periods of sodium and water loading. In Figure 2 the most obvious change in plasma and fecal sodium concentrations occurs after water loading induced by the infusion of 5 per cent glucose in water at the rate of 30 ml. per minute for 180 minutes. There is a sharp drop in plasma sodium after one hour but the decrease in fecal sodium does not occur for an additional two hours. Plasma and fecal osmolarities parallel these changes. Observed mouth to anus transit time with carmine dye in this patient was three and one-half hours. In Figure 3 there are less striking changes in plasma and fecal sodium levels but the values show a close degree of correlation. Plasma osmolarity increased sharply with a sodium load of 265 mEq. per hour; fecal osmolarities showed similar increases. Observed mouth to anus transit time in this patient was two hours.

From data obtained on 10 patients it was possible to calculate the extent of plasma CO_2 elevation after infusions of sodium bicarbonate solution. The relationship of the amount of sodium bicarbonate infused to increase in plasma CO_2 content is shown in Figure 4. It was determined that 0.46 to 0.8 mEq. of sodium bicarbonate per Kg. of body weight (mean 0.58) would raise the plasma CO_2 content 1 mEq. per L. These values are not corrected for fecal loss of HCO_3^- during the infusion period and indicate approximate sodium bicarbonate requirements for treating the acidosis of cholera patients who had an active diarrhea. Urinary HCO_3^- losses were assumed to be negligible because postinfusion elevation of plasma HCO_3^- did not exceed the normal range. There

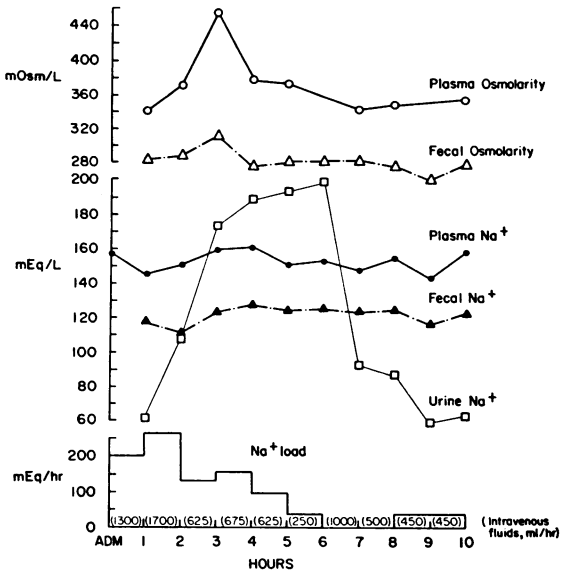

FIG. 3. PATIENT NO. 21; RESPONSE OF PLASMA, FECAL AND URINARY SODIUM AND PLASMA AND FECAL OSMOLARITY TO WATER LOADING

Between hours six and eight, 5 per cent dextrose in water was substituted for normal saline.

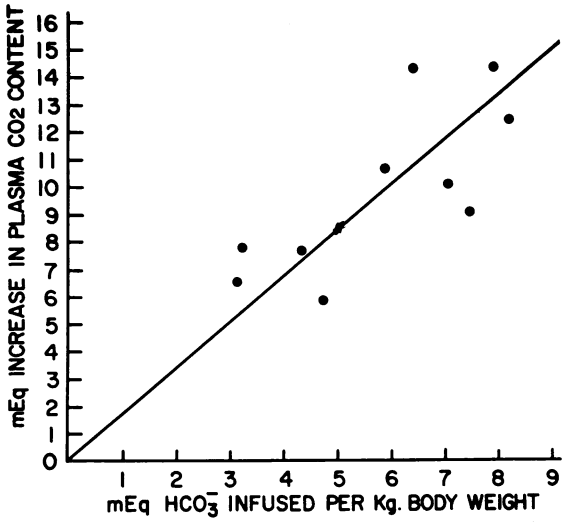

FIG. 4. RELATIONSHIP BETWEEN SODIUM BICARBONATE INFUSED AND RESULTING ELEVATION OF PLASMA CO_2 CONTENT

The line represents a plot of the mean value (0.58 mEq. per Kg.).

is evidence that urinary excretion of HCO_3^- is insignificant when plasma CO_2 levels are under 25 mEq. per L. (9). It was possible to correct for the fecal loss of HCO_3^- in several patients where fecal volume and fecal HCO_3^- concentration were known. Again, urinary loss of HCO_3^- was assumed to be negligible. In these patients it was found that a mean value of 0.41 mEq. per Kg. of infused HCO_3^- as sodium bicarbonate caused an increase of plasma CO_2 of 1 mEq. per L.

DISCUSSION

The necessity for fluid and electrolyte replacement in acute cholera is obvious. However, published literature provides no unanimity of opinion on how much fluid and how much electrolyte should be given because balance-type studies relating fecal to plasma concentrations in patients deprived of oral intake and given only intravenous fluids have not been reported heretofore. Referring to Table I, 24 hour fecal volumes averaged over 8 L. in the more severe cases. Total stool volumes during the two or three days of diarrhea averaged over 13 L. Although several 24 hour urine volumes are low, these were due to maintenance of minimal hydration; no patient in this series had evidence of ischemic renal damage. Urine output was found to be a reliable index of hydration because adequate renal function was established following infusions sufficient to lower Gp below 1.027.

The degree of dehydration in cholera patients cannot be estimated with accuracy by clinical signs but must be determined by measurement of hemoconcentration. Hemoglobin concentration and hematocrit have been found unreliable because cholera patients are not infrequently anemic (5). Admission electrolyte determinations are also of no assistance in assessing the severity of dehydration. Plasma sodium concentrations were usually higher in patients who were more severely dehydrated on admission but no correlation between plasma sodium levels and Gp was apparent in patients with Gp under 1.035. Comparison of Tables II and III also indicates no correlation between concentration of other electrolytes and the varying degrees of dehydration observed.

Plasma protein concentration was found to be a reliable guide to the extent of dehydration because convalescent plasma protein concentrations varied less from patient to patient than hemoglobin or hematocrit. The copper sulfate method (2) for determining plasma proteins was used during this study because of its accuracy, simplicity and adaptability to field conditions.

The volume of intravenous fluids required to maintain hydration during the first 24 hours of treatment varied from 3.5 to 21 L. The average patient required a total of 16 L. of fluids during his entire illness with a range of 6 to 35 L. The rapid prolonged loss of fluid of high electrolyte content which persisted for two to three days required the continuous replacement of water and electrolytes.

Much emphasis has been placed on the observation of low serum and blood chlorides in acute cholera patients. Rogers (10) in 1909 found lower blood chlorides in fatal cholera patients than in healthy Indians and postulated that more salt than water was lost in the feces. This reasoning led him to advocate the use of hypertonic (1.35 per cent) sodium chloride solutions which would he stated, "maintain the conservative beneficial hypertonicity of the blood, which would tend to carry more fluid into the circulation instead of removing it through the damaged bowel wall." The reporting of low plasma electrolyte concentrations by Rogers and by others is to be expected, since they reported their results as concentrations per volume of plasma or serum without correcting for the large amounts of plasma proteins in the blood of severely dehydrated cholera patients. In this study, several patients had low plasma chloride concentrations before correction for plasma protein content. While plasma measurements here have been corrected for protein concentration, such correction has been ignored in the reporting of electrolytes and osmolarity in the feces (which were all Seitz filtered) as the concentration of protein in Seitz filtered cholera stools is negligible, averaging from 0.1 Gm. per 100 ml. (Weaver, Johnson and Phillips) (1) to 0.2 Gm. per 100 ml. (Saha and Das) (11).

As long ago as 1849, Becquerel (12) postulated that the feces in cholera were a transudate that poured out through the damaged bowel wall. Nearly all writers on cholera who have studied the nature and composition of cholera stools have adopted this view. The most complete recent study of untreated cholera patients has been reported by Saha and Das (11) who injected sodium thiocyanate into patients with acute cholera and were able to detect this material in every sample of stool examined one to two hours after the injection. They also administered the blue dye T-1824 to several patients but were unable to recover it in the stool. They include studies of the biochemical composition of cholera feces obtained at admission prior to any treatment and found an average of 125 mEq. per L. of sodium, 76 mEq. per L. of chloride, 19 mEq. per L. of potassium and 31 mEq. per L. of bicarbonate (measured as CO_2 content). In only two of their 23 patients were all of these electrolytes determined on the same patient and simultaneous plasma determinations were not reported. From their studies they concluded that the cholera stool is a transudate from the plasma.

In the present study, fecal sodium and chloride concentrations, and fecal osmolarity, are consistently lower than their plasma values. Fecal potassium and HCO_3^-, however, are found in greater concentrations than in plasma, potassium being two- to sixfold and HCO_3^- nearly double the plasma levels. It is evident (Tables I and IV) that as 24 hour stool volumes increase, potassium concentrations decrease and the lowest values are found in patients with the most severe diarrhea. Fecal bicarbonate concentrations do not appear to be as closely related to fecal volume as the other ions. High concentrations of potassium (11, 13–15) and bicarbonate (11, 14) in diarrheal stools have been reported previously and are not unique to cholera.

In the adult, fecal excreta normally contain some potassium but almost no sodium and chloride (Elkinton and Danowski) (16) due to absorption of these ions in the lower ileum and colon. With the onset of diarrhea the concentrations of sodium and chloride in the feces increase in proportion to the fecal volume and approach plasma levels when the volume of excreta is over 3 L. per 24 hours (Tables I and IV). Increasingly rapid intestinal transit time as a result of larger stool volumes probably contributed to these elevated values by allowing insufficient time for reabsorption, but the extent of this contribution is unknown. Mouth to anus transit time with orally administered carmine dye was 90 and 150 minutes in two patients with over 8 L. of fecal excreta per 24 hours and 225 and 240 minutes in two cases with 24 hour fecal volumes of under 3 L. These observations indicate that transit time is shortened as fecal volume is increased and that sodium and

chloride conservation in the intestinal tract is related inversely to transit time.

Further evidence of the existence and variability of gastrointestinal potassium losses in abnormal conditions is supplied by the observations of Bernstein and colleagues (17) who produced diarrhea in uremic patients by perfusing the entire gastrointestinal tract with electrolyte solutions. Elevation of potassium levels in the intestinal perfusate in excess of the starting concentration was evident in most of their patients. In addition, the elevation of potassium in the intestinal perfusate was greater at a flow of 1 L. per hour than it was at 3 L. per hour.

Experimental studies in recent years have altered classical concepts of electrolyte movement and exchange in the mammalian gastrointestinal tract. In acute and chronic experiments in dogs, D'Agostino, Leadbetter and Schwartz (18) prepared colonic pouches into which they instilled isotonic saline. Specimens taken at frequent intervals during the following eight hours demonstrated that as sodium and chloride concentrations fell, potassium and HCO_3^- increased. Potassium concentrations reached an average of 15 to 20 mEq. per L. within three to four hours with little if any further increase. Bicarbonate concentrations increased steadily for the first four to five hours levelling off at CO_2 content of 50 to 70 mMoles per L. Comparable results were obtained when experiments were repeated after the colonic pouch had been treated with antibiotics. Visscher and co-workers (19, 20), using a sodium isotope and deuterium in dogs, have shown that this ion and water move in both directions across the intestinal epithelium even against large concentration gradients. They estimated that the total turnover rate of sodium was quite large, being approximately equal to the total plasma sodium every 83 minutes.

The origin of the copious diarrhea in cholera is not known. Nor is there any information regarding the site and extent of water and electrolyte exchange between the extracellular fluid and the gut lumen in this disease. It remains to be determined if the diarrhea fluid in cholera is the result of: *1*) a transudative process; *2*) an increase of normal gastrointestinal secretions; *3*) failure of normal water and electrolyte reabsorption; or *4*) a combination of these abnormalities. The transudate theory has been used for many years to explain the large fecal volumes in cholera. Reports of autopsy findings reviewed by Pollitzer (21), in which desquamation of the intestinal mucosa has been described, lends support to this concept. It is difficult, however, to reconcile the rapid return of bowel function, in patients recovering from cholera, with widespread mucosal damage; hence other diarrhea-provoking mechanisms should be considered.

Alteration of the reabsorptive capacity of the bowel by the *V. comma* could explain the source of the large fecal volumes if the transfer of water and electrolytes into the gut is not impaired. Using Visscher's figure of 83 minutes for clearance of sodium from the plasma, and assuming plasma volume to be 5 per cent of body weight, then, in a 55 Kg. man, the bowel would receive about 48 L. of isotonic fluid in 24 hours. Patient 15 (Table I) had a fecal volume in excess of 17 L. in 24 hours and, if this mechanism applies, it would indicate a 35 per cent impairment in the efficiency of his reabsorptive mechanism. In cholera it is quite obvious that reabsorption of fluids from the gut lumen is not normal and while transit time is rapid it is doubtful that decreased transit time is solely responsible for the diarrhea. On the other hand, if reabsorption were to be inhibited to varying degrees by the *V. comma* or its products, Visscher's studies provide a simple mechanism to explain the origin of the diarrhea fluid.

A close relationship between plasma and fecal electrolyte concentrations is evident in Figure 1. The same relationship exists in Figures 2 and 3 but of a smaller magnitude and with a lag in fecal concentrations presumably due to slower evacuation of the fecal volume. The renal response to both water and salt loading in preserving plasma sodium levels is demonstrated in Figures 2 and 3. It is also evident that while water and salt loading cause corresponding changes in fecal electrolytes, the bowel does not approach the kidney in ability for selective excretion of water and electrolytes.

Quantitative requirements for the treatment of acidosis were studied by infusing varying amounts of sodium bicarbonate into several cholera patients and observing changes in the plasma CO_2 content. Palmer and Van Slyke (22), reported that a 70 Kg. man would require 1.8 Gm. of oral sodium bicarbonate to elevate the plasma CO_2

concentration one volume per cent (0.69 mEq. per Kg. for 1 mEq. increase in HCO_3^-). Hence they assumed HCO_3^- to be distributed equally in total body water. In this study the infusion of 0.58 mEq. of sodium bicarbonate per Kg. body weight was required to increase plasma CO_2 content 1 mEq. (Figure 4). If corrections are made for the amount of HCO_3^- lost in the feces during the infusion period, a mean value of 0.41 mEq. per Kg. is found. This is identical with the value found following rapid infusion (100 ml. per minute) of a 4 per cent bicarbonate solution into patients without diarrhea during convalescence from typhoid fever (23).

In the present cholera study, bicarbonate was not given until the patients had been rehydrated. In these patients, assuming that extracellular water is 20 per cent and cellular water is 40 per cent of total body weight and that HCO_3^- is distributed equally throughout extracellular water, then for each mEq. increase of HCO_3^- in extracellular water, total cellular water will show an increase of only 0.5 mEq. The observation that the infusion of 0.41 mEq. of HCO_3^- per Kg. body weight will elevate plasma HCO_3^- by 1 mEq. is in accord with more recent observations in the literature. Pitts has reported (9) that the intravenous infusion of 15.7 mMoles of sodium bicarbonate per Kg. body weight into a nephrectomized dog will result in plasma HCO_3^- of 33.8 mEq. per L. or 0.46 mEq. per Kg. for 1 mEq. elevation per L. of plasma.

Singer and associates (24) infused hypertonic (0.89 molar) sodium bicarbonate into 12 normal subjects. Calculations from their data presented in Figure 3 indicate that the infusion of 0.46 mEq. per Kg. body weight resulted in the elevation of plasma HCO_3^- by 1 mEq. per L. However, in their discussion they stated that 0.35 mEq. per Kg. was a more representative value for their experiments. The present studies do not provide information as to the distribution of HCO_3^- ions in body fluids. This has been carefully studied and discussed by Singer and associates (24) and by Pitts (9). The present studies provide, rather, additional information on the quantity of sodium bicarbonate required to treat acidosis in patients with and without diarrhea.

The loss of large amounts of electrolyte in the feces of cholera patients indicates the necessity for adequate replacement. In addition to the sodium and chloride loss it is evident from Table I that for each liter of feces lost from cholera patients, an average of 45 mEq. of HCO_3^- and 16 mEq. of potassium should be given. From the elevated sodium concentrations and osmolarity values observed on admission and during treatment with isotonic saline (Tables I and II) evidence is provided that treatment with hypertonic solutions is not necessary and may be harmful, particularly in the presence of impaired renal function or low cardiac reserve. There is also sufficient evidence to condemn the use of nonelectrolyte solutions as the chief replacement fluid in cholera. Two patients (23 and 24, Table III) were initially rehydrated with 5 per cent dextrose in water. Low plasma sodium levels were observed at the end of the rehydration period and Patient 24 developed severe muscular cramps which were not relieved until 200 ml. of a 2 per cent solution of NaCl had been infused.

For the first time detailed, quantitative information has been provided on the water and electrolyte losses in cholera. However, the extent of water and electrolyte shifts between cellular and extracellular spaces cannot be determined from our data; this must await further study on cholera victims.

SUMMARY

1. Twenty-five patients with diarrhea were studied during the 1958 Bangkok cholera epidemic; 17 were proven to have had cholera. For the first 24 hours after admission patients were given nothing by mouth. During this period the infusion of intravenous electrolyte solutions was related to hydration and electrolyte concentrations in plasma, feces and urine.

2. Hyperosmolarity and elevation of plasma sodium and chloride were found on admission. Fecal osmolarity and fecal sodium and chloride concentrations were lower than corresponding plasma values while fecal potassium and bicarbonate levels were considerably higher.

3. The relationship between fecal electrolyte concentrations, volume and transit time is presented, and the significance of these findings in relation to experimental studies on active transport in bowel is discussed.

4. In correcting the acidosis of cholera the infusion of 0.58 mEq. of HCO_3^- as sodium bicarbo-

nate effected an elevation of plasma CO_2 of 1 mEq. per L. When correction for the fecal loss of HCO_3^- during the infusion period was made, this value was found to be 0.41 mEq. per Kg.

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