Electrolyte Economy and Its Hormonal Regulation in Congenital Chloride Diarrhea

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Summary

The economy of Cl^- , K^+ , and Mg^{++} , extracellular volume (ECV) and plasma volume, and the role of hyperreninemia and hyperaldosteronism were explored in 22 patients with congenital chloride diarrhea. Stool volume was in significant correlation with its Cl^- , Na^+ and K^+ content, the correlation being significantly better with Cl^- content than with the Na^+ content. Low fecal Cl^- concentrations were seen in chronic hypochloremic contraction, but acute episodes did not cause reduction of fecal Cl^- concentration from the basal level of 140–150 mmol/liter. The adequate condition (defined as normal serum electrolyte concentrations and blood pH, and presence of Cl^- in urine) was associated with high total exchangeable Cl^- and ECV. This excess Cl^- and ECV roughly equalled the high daily fecal amount of Cl^- and volume. Reduced ECV was accompanied by high renin activities and hyperaldosteronism, but in the adequate condition these were normal. Hyperaldosteronism caused a decrease in urinary $\text{Na}^+\text{-K}^+$ ratio and, after the age of 2–6 months, in the fecal $\text{Na}^+\text{-K}^+$ ratio. Total exchangeable K^+ was normal in the adequate condition. No Mg^{++} depletion was present, although the patients lack Mg^{++} substitution. The adequate condition could be maintained with an oral supplement of NaCl, KCl and water.

Speculation

Hyperreninemia, hyperaldosteronism, and hypokalemic alkalosis in congenital chloride diarrhea (CCD) are secondary to hypochloremic ECV contraction and can be completely corrected with adequate substitution. Mg^{++} depletion does not play a part in CCD. The intestinal response to hyperaldosteronism appears later in the intestine than in the kidney in the newborn CCD patient and presumably also in the normal newborn.

Congenital chloride diarrhea is caused by an inborn error in the intestinal Cl^- transport. Perfusion studies have shown that the active $\text{Cl}^-/\text{HCO}_3^-$ exchange of the ileum and the colon is defective (3, 17, 30, 36). This results in osmotic diarrhea with high fecal Cl^- concentration and acidity.

The characteristic state of CCD patients is hypochloremic, hypokalemic metabolic alkalosis, with high renin activity, hyperaldosteronism, and impaired renal function (9, 11, 13, 14, 18, 30). It has been suggested that K^+ depletion contributes to the intestinal absorption defect (11), and the renal pathology of CCD resembles that of experimental Mg^{++} depletion (25).

As CCD is a "Finnish disease," it has been the object of a long term investigation at this hospital (17–19, 23, 27–29, 31). For further characterization of the fluid and electrolyte derangement in CCD the following aspects were investigated: the economy of Cl^- , K^+ , and Mg^{++} , ECV and plasma volume (PV), and the role of hyperreninemia and hyperaldosteronism.

SUBJECTS

Twenty-two patients, aged 0.5–14.5 years (18), were studied. Their early long term substitution was with a 0.15–0.3 M water solution of KCl only, the dose (45–204 mmol/m²/24 hr) being adjusted to maintain normal serum electrolyte concentrations. Several episodes of acute dehydration had occurred lasting up to a week during the first years of life, but the subsequent clinical condition of the patients had been good. They passed a constantly Cl^- -free urine and tended to be slightly alkalotic.

Five years ago the therapy was changed to a 0.15–0.3 M NaCl + KCl solution with the molar ratio of the salts individually varying from 3:1 to 1:1. The dose was 60–216 mmol/m² daily and was adjusted to maintain chloriduria in addition to normal serum electrolyte concentrations and blood pH. Such a state will be referred to as the adequate condition.

The recordings of low serum electrolyte concentrations and alkalosis in this study were obtained from observations during acute exacerbations of the diarrhea, due to respiratory and gastrointestinal infections, and from observations in our early patients.

METHODS

Serum electrolyte concentrations and blood pH were measured according to standard methods. Urinary and fecal electrolyte excretion was always measured from 24-hr collections.

For measurement of total exchangeable Cl^- (TECl^-), 0.3 $\mu\text{Ci/kg}$ of ^{36}Cl , NaCl solution ($>3 \text{ mCi/g Cl}^-$) was injected intravenously with 5% glucose. Urines and stools were collected and after an equilibration time of 24 hr a spot plasma sample was taken. The specific activity in plasma Cl^- was measured and used in the calculations (37). Because biologic half-life of Cl^- is short in CCD, the radiation dose was minimal.

ECV was calculated as the "corrected Cl^- space" (6) from the same $^{36}\text{Cl}^-$ measurements. PV was measured with human serum [^{125}I]albumin (34).

Plasma renin activity was measured with radioimmunoassay (12) from samples taken in the supine position between 8 and 9 AM after an 8-hr fast. Urinary aldosterone excretion was measured from 24-hr urine with radioimmunoassay (1).

For measurement of total exchangeable K^+ (TEP) 3.5 $\mu\text{Ci/kg}$ [^{42}K]KCl solution (300 $\mu\text{Ci/g K}^+$) in 5% glucose was injected intravenously. After an equilibration time of 24 hr, during which urines and stools were collected, a spot urine sample was taken. The specific activity in urine K^+ was measured and used in the calculations (7).

Serum and erythrocyte Mg^{++} were measured according to standard methods (38). Muscle biopsies were taken according to the method of Bergström (2). Muscle Mg^{++} content was determined with neutron activation analysis (39), and expressed in mEq/100 g fat-free solids (FFS). For study of Mg^{++} economy, Thoren's test was employed (35).

RESULTS

CHLORIDE ECONOMY

The daily stool volume correlated with its Cl^- , Na^+ , and K^+ content ($r = 0.89$ for Cl^- , 0.82 for Na^+ , and 0.66 for K^+ , $n = 113$). This is to be expected because water is known to follow passively the movement of solutes in the intestine (8). When the serum electrolyte concentrations were normal the fecal Cl^- concentration was usually 140–150 mmol/liter. The correlation of volume was significantly better with the Cl^- content than with the Na^+ content, which is also to be expected as the primary disturbance is one of active Cl^- transport.

The fecal Cl^- content showed a correlation with the serum Cl^- concentration ($r = 0.42$, $n = 102$), Figure 1. Low fecal Cl^- concentrations were seen in patients who had been without substitution or on a small substitution dose for a long time and were hypochloremic. An extreme example was patient *JH* who, after a trial of substitution with K^+ -lactate, had a fecal Cl^- concentration of only 40 mmol/liter (Table 2). His clinical condition was, however, miserable. Acute episodes of hypochloremia did not cause any reduction in fecal Cl^- concentration (Fig. 2).

Fig. 1. Relationship of the amount of Cl^- in 24-hr stool ($dF\text{-Cl}$) and the serum Cl^- ($S\text{-Cl}$) concentration in patients with CCD.

Fig. 2. Relationship of the concentration of Cl^- in 24-hr stool ($dF\text{-Cl}$) and the serum Cl^- ($S\text{-Cl}$) concentration in patients with CCD.

Fig. 3. TECl and TEP in patients with CCD. ●: NaCl + KCl substitution; ▼: KCl substitution.

Fig. 4. Relationship of serum Cl^- ($S\text{-Cl}$) concentration and ECV measured as the "corrected Cl^- space" (Cl-Space) in patients with CCD.

The mean TECl^- , measured in four patients (23–33 kg), was 30.7 mmol/kg (range 28.1–33.8 mmol/kg) during hypochloremia. In 14 patients (10–33 kg) in the adequate condition it was 40 mmol/kg (Fig. 3). This is high compared with the 34.6 ± 1.6 mmol/kg (mean $\pm$ SD) predicted for their weight according to the calculations of Cheek and Graystone (5). In two 1-month-old infants TECl^- was even higher, 61.0 and 71.0 mmol/kg (mean normal 50.7 and 45.6 mmol/kg, respectively).

ECV AND PV, RENIN AND ALDOSTERONE

ECV was also high in these patients. For six patients who weighed more than 20 kg the mean "excess ECV" (actual ECV less the mean ECV calculated for body weight) was 1.1 liter. This roughly equalled their daily fecal volume. In the above-mentioned two infants the ECV was 46.1% and 49.5%, respectively (mean normal 30%). A decrease in serum Cl^- concentration was constantly accompanied by a contraction of ECV (Fig. 4). Urinary excretion of Cl^- always ceased when serum Cl^- concentration fell below 95 mmol/liter (18). Achloriduria is thus an indicator of hypovolemia.

PV was measured in seven patients together with ECV and plasma renin activity (Table 1). PV was mostly normal. A subnormal recording in patient *AS* was associated with "normal" ECV, achloriduria, and elevated renin activity. PV recordings at the lower normal range (*MK* and *PI*) were accompanied by a slight rise in renin activity and sparse chloriduria. Normal recordings were accompanied by high ECV, chloriduria, and normal to "high normal" renin activities.

Table 1. Indices of ECV in seven CCD patients

Subjects	Wt, kg	Urinary Cl ⁻ , mmol/24 hr	PV, ml/kg	ECV, %	Serum Cl ⁻ , mmol/liter	Plasma renin activity, $\mu\text{g/l/hr}$
AS	25	0.0	28.7	29.0	96	4.7
MK	33	3.0	38.5	25.0	96	6.1
PI	16	23.8	36.1	31.6	103	4.8
RKo	33	14.5	40.6	30.3	105	1.7
MV	23	34.8	48.4	29.3	109	1.6
LI	20	85.4	40.7	30.5	101	3.1
MH	17	84.2	56.5	32.3	110	3.0
Normal values			38-48	25.0	93-113	0.9-2.0

Fig. 5. Relationship of plasma renin (*P-Renin*) activity and the excretion of Cl⁻ in 24-hr urine (*dU-Cl*) in patients with CCD.

As chloriduria is an indicator of the volemia in CCD, plasma renin activity was plotted against 24-hr urinary Cl⁻ excretion (Fig. 5). With substantial chloriduria plasma renin activities were normal, whereas low or lacking chloriduria, that is reduced ECV, was accompanied by high renin activities. When urinary 24-hr aldosterone excretion was plotted against the chloriduria the same pattern was seen (Fig. 6). Hyperaldosteronism was seen only when chloriduria was low or lacking.

ALDOSTERONE EFFECT

Hyperaldosteronism was accompanied by a decrease in urinary Na⁺-K⁺ ratio indicating a normal renal response to aldosterone (Fig. 7). Normally, the distal intestine responds similarly to aldosterone (32). To investigate whether this occurs in the CCD patients, a correlation between the fecal Na⁺-K⁺ ratio and the urinary Na⁺-K⁺ ratio was sought. No such correlation was found in children below 6 months of age ($r = -0.06$, $n = 32$), but a clear correlation was present in the older children ($r = 0.37$, $P < 0.01$). Thus an intestinal response to hyperaldosteronism, a decrease in the fecal Na⁺-K⁺ ratio, was recorded, but only after the age of 6 months. The young infants did have hyperaldosteronism: urinary aldosterone excretions up to 59 $\mu\text{g/m}^2/24$ hr were recorded. Lack of the intestinal response during the first months suggest that it matures later than the renal response.

Urinary and fecal Na⁺-K⁺ ratios of patients in chronic dehydration are given in Table 2. Although already 6-9 months old, two of these patients had a higher Na⁺-K⁺ ratio in the stools

Fig. 6. Relationship of daily urinary aldosterone (*dU-Aldosterone*) excretion and the excretion of Cl⁻ in 24-hr urine (*dU-Cl*) in patients with CCD.

than in the urine. Three others, aged 9-30 months, had similar ratios in urine and stools. On the other hand, *JH* had a low fecal ratio at the age of 2 months. This might reflect an exceptionally early maturation of the intestinal response or a very high aldosterone activity. His aldosterone excretion was high, 55 $\mu\text{g/m}^2/24$ hr.

POTASSIUM ECONOMY

TEP was measured on 39 occasions in patients who were in "the adequate condition." TEP was normal in all children, who were older than 1 year, whether substituted with KCl or NaCl + KCl (Fig. 3). In the younger infants some subnormal values were recorded, although their serum K⁺ concentrations were normal. The lowest TEP value recorded was in patient *JK* who had been on a 0.9% NaCl-0.2% KCl solution until the age of 6 months because he showed a tendency to hyponatremia and hyperkalemia when newborn on our usual 0.7% NaCl-0.3% KCl solution. When switched back to the latter solution his TEP became normal. The second lowest value in the same group was of patient *HP*, who was slightly alkalotic and without chloriduria. As his dose was increased TEP normalized.

Mg⁺⁺ ECONOMY

A total of 22 determinations of serum Mg⁺⁺ concentration was obtained from 13 patients. The levels ranged from 0.73-1.06 mmol/liter (normal range 0.7-1.0 mmol/liter), with a mean of 0.88 mmol/liter. Erythrocyte Mg⁺⁺ concentration, determined 22 times from 11 patients, was 2.1-3.09 mmol/liter (normal range 2.43-2.85 mmol/liter); the mean was 2.52 mmol/liter. Of 0.5 mEq Mg⁺⁺/kg infused intravenously into eight patients, the mean of 70% was excreted in urine in 24 hr. Only

two patients excreted less than 60% (40 and 56%). The retention of more than 60% of the dose is considered to be a clear sign of Mg^{++} depletion (16).

Muscle biopsies were taken from seven patients (including the two with less than 60% excretion) and two healthy control subjects, a 7.4-year-old girl and an adult male. The control subjects had muscle Mg^{++} concentrations of 6.6 and 8.6 mEq/100 g FFS, respectively, both within the normal range (10, 26). The patients' values ranged from 6.6–10.6, mean 8.8 mEq/100 g FFS. Because no low values were recorded, it is concluded that CCD does not cause Mg^{++} depletion.

DISCUSSION

The adequate condition was accompanied by high $TECl^-$ and ECV in our patients. This seems to be a feature of the optimal state of CCD patients. The "excess" Cl^- and EC fluid obviously is made up of the large intestinal content of Cl^- and water in this disease. In agreement with this is our observation that the excess Cl^- and EC fluid in the older patients was of the same magnitude as their daily fecal Cl^- and volume. The $TECl^-$ and ECV were proportionately even larger in our infants, and so were their daily stool volumes (about 200 ml for their weight of 2000 g in contrast to 1100 ml for 30 kg). Normal $TECl^-$ and ECV have previously been recorded in CCD patients (20, 24, 30), but these were usually associated with achloriduria and/or high hormonal activities, and thus, presumably with decreased real ECV.

It is clearly shown by the present investigation that the high renin activities and hyperaldosteronism appear only in ECV contraction. Achloriduria, which was formerly regarded as an inevitable feature of CCD, is also a result of the contraction. With proper substitution normal ECV and PV can be maintained, and this adequate condition is associated with normal plasma renin activity, normal urinary aldosterone excretion,

and chloriduria. Chloriduria is a convenient indicator of the adequacy of the therapy.

In the newborn normal aldosterone production was recorded (18) with the normal renal response seen as reversal of the urinary Na^+K^+ ratio. The fecal Na^+K^+ ratio did not change in the first months of life, but later a clear decrease was documented. Probably because of lateness (1) of intestinal response to aldosterone resulting in enhanced Na^+ absorption and (2) of the appearance (secretion?) in the intestine of NH_3 which binds the H^+ secreted in exchange for Na^+ (18), "the typical stool composition of CCD" with a Cl^- concentration exceeding the sum of Na^+ and K^+ appears only after the first months of life. With insufficient substitution the newborn developed a hypotonic contraction, whereas the older children maintained normal Na^+ concentration (18), but at the cost of renal (and intestinal) K^+ loss and alkalosis. This is also in agreement with the slow maturation of aldosterone response.

Hypokalemia has been a very common finding in CCD. An impairment of K^+ transport has even been proposed for the basic defect (21), and many authors have underlined that K^+ depletion may further reduce a primarily disturbed Cl^- absorption (11, 20). Thus, substitution with KCl alone was the rule in the first cases described. Our perfusion studies of the colon in three CCD patients revealed a larger than normal K^+ loss, and this was explained as secretion of K^+ along with H^+ in exchange for Na^+ (17). The present results show that TEP was normal in most of our patients on both KCl and NaCl + KCl substitution. Low TEP values were recorded among the younger children during inadequate substitution; the values normalized on increasing the daily K^+ dose. Normal TEP can thus be maintained with a substitution that compensates for the fecal loss and inhibits hyperaldosteronism.

The hypokalemic alkalosis of inadequately substituted patients is the result of three factors. (1) The hypochloremia caused by the fecal loss of Cl^- results in reduced delivery of Cl^- to the renal tubules. Thus, more HCO_3^- is absorbed with Na^+ , presumably both in the proximal and distal tubules (HCO_3^- absorption and H^+ secretion). (2) The contraction of ECV increases the maximal HCO_3^- reabsorption (33). (3) Hyperaldosteronism enhances renal (22) and intestinal (32) K^+ loss, and K^+ depletion further increases the alkalosis (33). To correct the derangement, the hypochloremia, the contraction, and the K^+ depletion must all be treated.

An Mg^{++} depletion is known to accompany chronic diarrhea (16, 35). It has also been reported in one CCD patient (15), and low urinary excretion of Mg^{++} was recorded in our patients (18). Furthermore, as the renal lesion in CCD resembled the one seen in experimental Mg^{++} depletion, we had to consider Mg^{++} depletion as a feature complicating CCD. However, according to the present findings, Mg^{++} economy is normal in CCD patients on adequate NaCl-KCl substitution, and magnesium depletion is an unlikely etiologic factor of the renal lesion.

The pathophysiology of CCD seems to be largely established. The primary disturbance is an inborn error of metabolism which results in a defect of the active Cl^-/HCO_3^- exchange in the

Fig. 7. Relationship of the Na^+K^+ ratio in 24-hr urine ($dU-Na/K$) and the daily urinary aldosterone ($dU-Aldosterone$) excretion in patient SA.

Table 2. Serum electrolyte concentrations, base excess (BE), and 24-hr urinary and fecal excretion of Na^+ , K^+ , and Cl^- and Na^+K^+ ratio in six CCD patients after chronic contraction and hypoelectrolytemia of several weeks' duration

Subjects	Age, mo	Serum (blood), mmol/liter				Urine, mmol	Feces, mmol	Treatment, mmol Cl ⁻ /m ² /24 hr
		Na ⁺	K ⁺	Cl ⁻	BE	Na ⁺ /K ⁺ (Na ⁺ ; K ⁺ ; Cl ⁻)	Na ⁺ /K ⁺ (Na ⁺ ; K ⁺ ; Cl ⁻)	
JT (n = 6) ¹	6	140	4.0	100	+7.2	0.13 (6.8; 39.1; 0.2)	1.88 (39.5; 21.2; 88)	142
AS (n = 5)	9	140	2.5	90	+15	0.07 (1.8; 26.2; 0.7)	1.27 (17.9; 14.5; 48)	82
RKo (n = 4)	9	135	2.5	85	+15	0.02 (0.4; 19.1; 0.2)	0.05 (8.3; 14.7; 35)	88
RJ (n = 9)	9	140	4.5	100	+5.2	0.77 (19.7; 26.1; 2.4)	0.83 (22.1; 26.8; 78)	
MK (n = 5)	30	135	4.5	115	+2.3	0.01 (0.2; 43.5; 0.4)	0.26 (15.8; 53.7; 88)	216
JH (n = 6)	2	120	2.5	70	+10	0.05 (0.0; 3.9; 0.0)	0.49 (4.9; 10.3; 6.4)	86 (K ⁺ -lactate)

¹ Number of measurements used in calculations.

ileum and the colon. The deficient absorption of Cl^- results in osmotic diarrhea. With deficient HCO_3^- secretion H^+ , which is secreted in exchange for Na^+ , accumulates in the intestinal contents and blocks further Na^+ absorption. If the intestinal electrolyte and water loss is not replaced, a hypochloremic ECV contraction develops, with high plasma renin activity and hyperaldosteronism. In the newborn with an immature response to aldosterone, the contraction is hypo-osmolal. If the infant survives, the renal Na^+ absorption and K^+ secretion are enhanced during the first weeks of life and normonatremia may recur spontaneously. Although urinary Cl^- is completely absorbed, hypochloremia, ECV contraction, and hyperaldosteronism persist during normal salt intake. A hypokalemic metabolic alkalosis is maintained. Through an intestinal response to hyperaldosteronism the fecal Na^+/K^+ ratio is reduced after the first months of life. When NH_3 appears in the intestine and binds the H^+ secreted in exchange for Na^+ , the fecal Cl^- concentration will exceed the sum of Na^+ and K^+ . If adequate substitution is not instituted most patients will die in the first months of life but some will survive with retarded development (18).

Because the proximal small intestine is permeable to Cl^- a normal state can be maintained with an oral replacement of the electrolytes and water lost in the stools. The dose has to be adjusted individually to maintain normal serum electrolyte concentrations, blood pH, and normal ECV. Chloriduria is a convenient indicator of the normality of ECV. In this "normal" state TECl^- and ECV, as regularly measured, are high. PV and renin activity, as well as aldosterone excretion, are normal. The diarrhea is thus maintained, but a completely normal development and social adjustment are possible (18).

CONCLUSION

The economy of Cl^- , K^+ , and Mg^{++} , ECV and PV, and the role of hyperreninemia and hyperaldosteronism were studied in 22 patients with CCD. The hypokalemic metabolic alkalosis and the high hormone activities were shown to be the result of hypochloremic contraction caused by intestinal Cl^- and water loss. An intestinal response to hyperaldosteronism was documented, but only after the first months of life. Mg^{++} economy was normal. Normal serum electrolyte concentrations and blood pH as well as normal ECV, PV, and hormone activities could be maintained with an oral supplement of NaCl , KCl , and water. Chloriduria is a convenient indicator of the normality of ECV, and thus of the adequacy of the Cl^- substitution dose.

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