The Mechanism of Hyperchloremic Acidosis During the Recovery Phase of Diabetic Ketoacidosis

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SUMMARY

To determine the mechanism of hyperchloremic acidosis during recovery from diabetic ketoacidosis (DKA), serial measurements were made in eight patients of serum and urinary electrolytes and organic acids, and of urinary net acid. On admission, the average decrease in serum total CO_2 was 17.5 mmol/L, corresponding to the excess anion gap, 18.5 meq/L, and the serum organic acids, 17.1 meq/L. With the treatment, the anion gap and organic acids decreased by 16.1 and 14.7 meq/L, respectively, but the serum CO_2 increased only by 8.4 mmol/L; serum electrolyte balance was maintained by increase in chloride concentration. Fluid retention was insufficient to explain the disparity between the increase in CO_2 and the decrease in organic acids. Renal loss of bicarbonate precursors during treatment was modest and was exceeded by renal bicarbonate production. The disparity between the increase in serum CO_2 and the decrease in organic acids during treatment of DKA may be explained to a large extent by a difference in volume of distribution between bicarbonate and organic anions. The renal loss of ketone anions before admission, however, is ultimately responsible for the persistence of substantial metabolic acidosis. DIABETES *30*:310–313, April 1981.

In the development of diabetic ketoacidosis, a large quantity of strong organic acid is titrated by intracellular and extracellular buffers. One obvious consequence of this process is a fall in serum bicarbonate concentration; another is the accumulation of salts of organic acids in the blood, leading to the establishment of an increased anion gap. A less obvious consequence of the buffering process is the conversion of intracellular nonbicarbonate buffers to the acid state ($BUF^- \rightarrow HBUF$). The restoration of normal acid-base balance requires the provision of sufficient alkali to back-titrate the cellular nonbicarbonate buffers and to reestablish simultaneously the normal intracellular and extracellular bicarbonate concentrations. The sources of bicarbonate for this process are bicarbonate generated in metabolism of ketone anions, the generation of bicarbonate by the kidney, and administration of bicarbonate by the physician.

In a previous study, it was shown that the disappearance of organic anions from the blood of treated patients with DKA was fairly regularly accompanied by a phase of hyperchloremia before the serum bicarbonate returned to normal.[1] The conclusion was offered that, before admission, the patients had lost in the urine a significant part of the ketone anions formed in the process of buffering, so that the complete conversion of the remainder of the ketone anion pool to bicarbonate was insufficient to restore serum bicarbonate to normal. The similarity, at admission, between the reduction in serum bicarbonate and the concentration of organic anions in serum, was regarded as coincidence; there is no requirement in organic acidosis that the excess anion gap be equal to the deficit in serum bicarbonate.[2]

Alternative explanations for the hyperchloremic phase included the dilution of extracellular bicarbonate by chloride-containing solutions, and the urinary loss of large quantities of bicarbonate precursor as ketonuria during the treatment phase. In the present study, the metabolic data collected include measurement of the loss of organic acid (keto acids and lactic acid) and the generation of bicarbonate by the kidney during the treatment of DKA. The results permit a better delineation of the mechanism of the transient hyperchloremic acidosis, and support the conclusions offered earlier that large amounts of bicarbonate precursor have been lost before admission. The data suggest that the volume of distribution of bicarbonate is higher than that of ketone anions.

PATIENT AND METHODS

The diagnosis of ketoacidosis was made in eight patients on the basis of a strongly positive reaction of serum to Acetest

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in the presence of metabolic acidosis and hyperglycemia. The diagnosis was confirmed by measurement of serum betahydroxybutyrate concentration. Arterial blood pH on admission was less than 7.25 in all patients. Treatment consisted of regular insulin administered either intramuscularly in doses of 10 U/h or by constant i.v. infusion at 5–10 U/h. Fluid was administered as 0.9% NaCl, 0.45% NaCl, or 5% dextrose, according to need. Potassium chloride and sodium bicarbonate were administered at the discretion of the house staff.

Before the start of therapy, measurements were made of serum betahydroxybutyrate, lactate, and total CO_2, and of arterial blood gases. The course of ketoacidosis was followed by serum Acetest reaction, with hourly measurement at first and later with measurement at 2–3-h intervals. Serum electrolytes and arterial blood gases were also measured at the same intervals. Urine was collected from the beginning of therapy until the serum Acetest reaction showed resolution of ketoacidosis, and at this point, the study was terminated. Serum betahydroxybutyrate concentrations at the end of the study were all less than 1.0 meq/L except one, which was 1.4 meq/L. The following measurements were made in the urine: Na, K, betahydroxybutyrate, lactate, NH_4, and titratable acid. Betahydroxybutyrate[3] and lactate (rapid lactate method, Calbiochem, La Jolla, California) were measured by enzymatic spectrophotometric methods. Na and K were measured by flame photometry, and Cl by potentiometric titration. Total CO_2 was measured by an osmometric technique.[4] Anion gap was calculated as Na − (Cl + CO_2), and the excess anion gap as the observed anion gap − normal anion gap (12 meq/L). Urinary NH_4 was measured by an osmometric technique[5] and titratable acid with a standard pH meter. Net acid excretion was calculated as (NH_4 + titratable acid) − bicarbonate. However, urinary bicarbonate concentrations were all too low to be measured. Acetoacetate was not measured directly but was estimated from betahydroxybutyrate by assuming the ratio of the former to the latter to be 1:3 in serum and 1:2.5 in urine.[6] The concentration of acetoacetate is sufficiently low that no meaningful error is introduced by this assumption. The contribution of HCO_3 by the kidney during the treatment period was calculated as net acid excretion − the sum of urinary acetoacetate, betahydroxybutyrate, and lactate.

RESULTS

On admission, the average blood pH was 7.06 ± 0.0, with a venous serum total CO_2 of 6.5 mmol/L ± 1.0. The reduction in serum total CO_2, 17.5 mmol/L ± 1.0 (calculated as normal total CO_2, 24 mmol/L − the measured serum CO_2), was approximately equal to total organic anions, 17.9 meq/L ± 0.8, and to the excess anion gap, 18.5 meq/L ± 0.9. With treatment, the arterial blood pH increased to 7.32 ± 0.0 and the serum total CO_2 to 14.9 mmol/L. During the same period, the anion gap decreased to 14.4 meq/L, while the organic acid concentration decreased to 2.4 meq/L. Thus, the persistent deficit in serum total CO_2, 9.1 mmol/L, greatly exceeded the excess anion gap, 2.4 meq/L, and the acidosis was then characterized by absolute or relative hyperchloremia (Table 1).

Table 2 shows sodium, potassium, and water balance, and the urinary excretion of organic acids and net acid. For the whole group, total organic acid excretion was 86.6 meq ± 20.3 and net acid excretion was 164.6 meq ± 27.7. The term "total organic acid" refers to the sum of the salt and acid form. During the balance period, the average amounts of water and sodium retained were 3.0 L and 402 meq/L, respectively. There was a net loss of 5 meq of potassium during the same period. Since there was little change in serum sodium during this period, the fluid therapy resulted in an increase of about 3 L of extracellular volume with essentially no change in intracellular volume.

Table 3 summarizes changes in acid-base parameters and bicarbonate balance during the period of urine collection. During this period, the anion gap and serum organic acid decreased by 16.1 meq/L ± 1.6 and 15.5 meq/L ± 1.2, respectively, but serum CO_2 increased by only 8.4 mmol/L ± 1.6. During the same period, the quantity of $NaHCO_3$ received by each patient was 34 meq ± 13, and the average amount of bicarbonate generated by the kidney was 78.1 meq ± 18.8.

DISCUSSION

Apart from administered bicarbonate, which in the present series of patients averaged 34 meq, the body buffers are returned to normal in DKA by bicarbonate from two sources: (1) the conversion of the total body pool of organic anions to bicarbonate, and (2) generation of bicarbonate by the kid-

TABLE 1
Serum organic acids and electrolyte and arterial blood pH on admission and following treatment*

	Betahydroxybutyrate		Acetoacetate		Lactate		Total organic acid		Na		K		Cl		CO_2		AG		Blood pH	
Patient	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
EL	13.9	0	4.8	0	3.5	1.2	22.2	1.2	132	134	4.2	3.6	96	108	5	18	31	8	7.00	7.33
AR	10.0	1.3	3.3	0.4	3.0	1.8	16.3	3.5	126	131	5.8	4.2	95	105	3	18	28	8	7.06	7.31
JB	8.9	0.7	3.0	0.2	3.2	3.2	15.1	4.1	132	133	4.6	4.7	89	97	12	16	31	20	7.22	7.31
FF	9.2	0.1	3.1	0	5.4	2.5	17.7	2.6	139	137	5.3	4.4	99	104	7	14	33	19	7.12	7.32
AJ	9.4	0.3	3.1	0.1	4.9	1.6	17.4	2.0	137	134	5.2	3.7	99	108	7	15	28	11	7.17	7.30
BW	10.0	0.3	3.3	0.1	3.4	1.7	16.7	2.1	133	137	6.9	4.6	96	106	5	17	32	14	7.10	7.43
MG	9.6	0.8	3.2	0.3	4.5	1.2	17.3	2.3	134	132	4.4	4.0	102	108	5	9	27	17	6.98	7.30
MC	12.8	0.1	4.3	0	3.3	1.2	20.2	1.3	130	137	4.8	3.5	88	107	8	12	34	18	7.02	7.31
Mean	10.5	0.5	3.5	0.1	3.9	1.8	17.9	2.4	133	134	5.2	4.1	96	105	6.5	14.9	30.5	14.4	7.06	7.32
SEM	0.6	0.2	0.2	0.0	0.3	0.3	0.8	0.4	1.4	0.8	0.3	0.2	1.7	1.3	1.0	1.1	0.9	1.7	0	0

AG = anion gap.
* All units are in meq/L except blood pH.

TABLE 2
Fluid balance, urinary organic acids, net acid excretion, and renal bicarbonate balance*

Patient	Fluid balance		Na balance		K balance		Beta-OH-butyrate	Aceto-acetate	Lactate	Total O.A.	UNH_4	T/A	Net acid	Net HCO_3 gain
	in	out	in	out	in	out								
EL	4	1.4	410	77	60	54	28.1	11.2	1.8	41.1	67.3	15.8	83.1	42.0
AR	3	2.2	333	173	0	68	64.0	25.6	9.5	99.1	177.3	51.6	228.9	129.8
JB	2.5	1.3	325	85	60	45	43.5	17.4	3.7	64.6	50.1	22.8	72.9	8.3
FF	6	2.9	495	183	0	78	22.3	8.9	13.3	44.5	174.0	34.8	208.8	164.3
AJ	6	1	675	54	90	25	29.4	11.8	1.6	42.8	64.1	20.7	84.8	42.0
BW	4.5	1.2	618	85	0	69	35.8	14.3	2.2	52.3	65.6	78.6	144.2	91.9
MC	6	1.8	540	91	90	57	124.1	49.6	5.6	179.3	118.6	104.0	222.6	43.3
MG	6.8	3.7	660	90	75	41	113.3	45.3	10.2	168.8	153.0	119.0	272.0	103.2
Mean	4.9	1.9	507	105	47	55	57.6	23.0	6.0	86.6	108.8	55.9	164.6	78.1
SEM	0.6	0.3	50	17	14	6	14.2	5.7	1.6	20.3	19.0	14.2	27.7	18.8

Total O.A. = total organic acids; UNH_4 = urinary ammonia; T/A = titratable acid.
* All units are in meq/balance period except fluid balance which is in L/balance period. Net HCO_3 gain = contribution of HCO_3 by the kidney, calculated as net acid minus urinary total O.A. The average duration of balance period was 12 h ± 3.0 SD with the range of 9–18 h.

ney through mechanisms other than the excretion of organic acids. Net acid excretion − total urinary organic acid was 78.1 meq, indicating that the kidney was a source of additional bicarbonate rather than bicarbonate loss during the treatment period. The endogenous production of the usual metabolic acids during the balance period is likely to be too small to alter the conclusions of the study. The average duration of the balance period was 12 ± 3 SD h with a range of 9–18 h.

The metabolic acidosis of our untreated diabetic patients was typically associated with an increased anion gap. The decrease in serum total CO_2 (17.5 mmol/L) almost exactly matched the excess anion gap (18.5 meq/L) and the organic anions (17.9 meq/L). The increase in serum total CO_2 with treatment (8.4 mmol/L) was much smaller than the decrease in anion gap (16.1 meq/L) and the decrease in organic anions (15.5 meq/L) during the same period. When the organic acid concentration of the serum falls close to normal levels with treatment, it must be assumed that essentially all of the excess organic acid anions present in the body on admission have been either excreted in the urine or converted to bicarbonate. However, the total body buffer deficit is still substantial at the end of the study period, as shown by the deficit in serum bicarbonate despite the addition of about 112 meq of exogenous and endogenous (renal) bicarbonate. Considering that only a small amount of organic acid was excreted in the urine during the treatment period (and some of that converted to bicarbonate in the process), the quantity of bicarbonate precursors in the body must have been far less than the buffer deficit at the time of admission. Since the buffer deficit was created by titration of organic acid, the quantity of the organic anion produced is equal to the buffer deficit generated. It follows that the difference between the alkali deficit and the organic anion retained in the body on admission represents the quantity of organic anion lost into the urine before admission to the hospital. It seems odd that the deficit in serum bicarbonate should be almost exactly balanced by the organic anion concentration, as there is so much disparity between the total alkali deficit and the total organic anion pool at the time of admission. This paradox could be explained by the fact that the alkali deficit includes a large requirement for titration of cellular buffers, in addition to the amount required to restore extracellular bicarbonate,[7,8] while the available organic anion could be largely confined to the extracellular space. In severe metabolic acidosis, the amount of bicarbonate required to increase serum bicarbonate concentration by a given extent is far greater than the amount predicted on the assumption that the administered bicarbonate will be uniformly distributed throughout the total body water. Thus, at the time of admission, the patients' serum bicarbonate concentrations tended to underestimate the total alkali deficit, while the serum organic anion concentrations tended to overestimate the quantity of potential bicarbonate. In other words, the "volume of distribution" of the organic anions was less than the "volume of distribution" of bicarbonate.

TABLE 3
Changes in acid-base parameters and bicarbonate balance with treatment

Serum total CO_2	8.4 mmol/L ± 1.6
Anion gap	16.1 meq/L ± 1.6
Serum organic acid	15.5 meq/L ± 1.2
HCO_3 received	34 meq ± 13
Net acid excretion	164.6 meq ± 27.7
Urinary organic acid	86.6 meq ± 20.3

Although the distribution of organic anions across cell membranes has not been extensively investigated, the influence of factors such as the transmembrane pH gradient (cell pH lower than extracellular pH) and the transmembrane electrical gradient would predict that cell concentrations are well below those of the extracellular fluid.[9,10] The distribution of betahydroxybutyrate and acetoacetate across the red cell membrane appears to vary with clinical states. Plasma concentration of ketones is higher in normal subjects, but in ketoacidosis, the concentration in the red cells may exceed that of plasma.[6] However, since the membrane potential of the red cells is about one-tenth the membrane potential of other cells, the red cell cannot be considered as representative of other tissues. If the distribution of ketone anions throughout the body were dependent on the transmembrane pH gradient, the cell concentration would be higher than if it were controlled by the transmembrane

electrical potential, but cell concentrations would still be much lower than plasma levels. In starved and alloxan-diabetic rats, the ratio of muscle intracellular water concentration to plasma water concentration of ketone bodies ranged from 0.47 to 0.30.[11] This suggests that the ketone body distribution across the muscle cell membrane is dependent on the transmembrane pH difference. Lactate appears to be distributed across the red cell membrane according to the Donnan equilibrium,[9] and if this held true for other tissues, overall cell lactate concentration should be extremely low. Since these organic anions are metabolizable, and since the sites of production and utilization are often different, the ketone anion concentrations might be lower and lactate concentrations higher in the muscle cells than the values predicted by the Donnan equilibrium or pH.

When the term "volume of distribution" is applied to bicarbonate, it has a meaning different from its application to any other substance. Whether administered or generated endogenously, bicarbonate must be used not only for increasing the extracellular and intracellular bicarbonate concentrations, but also for titration of the cellular and tissue buffers including bone. When bicarbonate titrates cellular and tissue buffers, the acquisition of H^+ converts it to H_2CO_3, which in turn becomes CO_2. The fact that bicarbonate is apparently distributed in a volume much larger than the total body water, despite the lower bicarbonate concentration in the cell than in the extracellular fluid, can be explained by the consumption of bicarbonate in cellular and tissue buffering.

The failure of serum bicarbonate to rise commensurately with the fall in organic anion can be explained to only a minor degree by expansion of the extracellular fluid. The average amount of fluid retained in the extracellular spaces was 3 L. This can only account for an increased bicarbonate requirement of about 45 meq, since serum total CO_2 at the end of the study period was 15 meq/L.

It is true that substantial amounts of chloride were retained during recovery from DKA, but chloride retention, while it contributed to the development of hyperchloremia, was not its sole cause; intracellular movement of water and shift of chloride from erthrocytes during buffering would elevate plasma chloride. The metabolic acidosis during the recovery phase is caused by the lack of adequate amounts of alkali, not the retention of Cl^-. Chloride solutions can cause metabolic acidosis only by dilution, i.e., expansion of the extracellular space with reduction in HCO_3 concentration. Studies of the phenomenon of dilution acidosis have shown that it produces only a very modest fall in serum HCO_3; e.g., in dogs whose extracellular fluid volume was expanded by 38% with isotonic saline, cellular buffering limited the decrease in serum HCO_3^- to only 10%.[12] The retention of 3 L of isotonic saline by our patients could explain only a very small part of the observed bicarbonate deficit.

The persistence of substantial acidosis, even after the nearly complete metabolism of organic anions and the generation by the kidney of more bicarbonate than it lost during the recovery phase, indicates that a substantial loss of bicarbonate precursors, ketone anions and lactate, had occurred before the patients were admitted to the hospital. If all of the organic anions produced through titration of the body buffers were retained in the body, i.e., if no renal loss had occurred, metabolism of these anions following treatment with insulin would have restored bicarbonate concentration to pre-illness levels, with a small reduction attributable to continuous production of usual endogenous acids. The fact that substantial reduction in bicarbonate concentration persisted after nearly complete metabolism of retained organic anions strongly indicates that substantial loss of organic anions occurred before admission to the hospital. Some reduction in bicarbonate concentration attributable to expansion of extracellular volume following admission does not alter this fact, since it merely represents the restoration of the volume that was lost during the early phase of DKA. The bicarbonate deficit at the time of admission was therefore much greater than the amount that could be made available through metabolism of the existing pool of organic anions. This fact was masked because the organic anions that were not excreted remained mostly in the extracellular fluid and, by coincidence, matched almost exactly the reduction in serum total CO_2.

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