Use of Sodium Concentration and Anion Gap to Improve Correlation Between Serum Chloride and Bicarbonate Concentrations

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Although most acid-base disorders cause opposite and equal changes in serum chloride and bicarbonate concentrations, this inverse relationship can be distorted by changes in the anion gap and/or water balance. Therefore, we examined the relationship between chloride and bicarbonate before and after adjusting for anion gap and serum sodium concentration. Patients with abnormal electrolytes were grouped by chloride and bicarbonate concentrations (low, normal, and high). Then, chloride and anion gap-adjusted bicarbonate were adjusted for water excess (or deficit), manifesting as hyponatremia (or hypernatremia), after which patients were reclassified. Classification by chloride and bicarbonate changed in 82% of the 135 patients after adjustment for anion

gap and sodium. Serum chloride and bicarbonate were each low (concordant) in 23 patients, while 18 had discordant chlorides and bicarbonates (9 low/high, 9 high/low). After adjustments, chloride and bicarbonate were discordant in 40 patients (31 low/high, 9 high/low) and concordant in none. The correlation between serum chloride and bicarbonate improved from -0.459 to -0.998 after adjustments for sodium and anion gap. A very close inverse relationship between serum chloride and bicarbonate concentrations is commonly distorted by concomitant water disturbances and anion gap acidoses in internal medicine patients admitted with electrolyte disorders. *J. Clin. Lab. Anal.* 20:154–159, 2006. © 2006 Wiley-Liss, Inc.

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INTRODUCTION

Clinicians commonly encounter four acid-base disorders (1–5): metabolic alkalosis, respiratory alkalosis, respiratory acidosis, and metabolic acidosis (the latter with normal or with increased anion gap). Metabolic alkalosis and respiratory acidosis lead to opposite changes in serum chloride and bicarbonate levels (specifically hypochloremia and hyperbicarbonatemia). Likewise, respiratory alkalosis and metabolic acidosis with normal anion gap also lead to opposite changes in serum chloride and bicarbonate levels (specifically hyperchloremia and hypobicarbonatemia).

In contrast to the types of patients just discussed, patients with metabolic acidosis with increased anion gap typically exhibit hypobicarbonatemia without hyperchloremia. Likewise, relative or absolute changes in water balance, resulting in hypo- or hypernatremia, can lower (or raise) both serum chloride and bicarbonate

concentrations by diluting (or concentrating) them in the extracellular fluid compartment. Disturbances of water balance, if profound, can lead to hypochloremia with hypobicarbonatemia or to hyperchloremia with hyperbicarbonatemia, even when no primary acid-base disorder is present. Thus, water disturbances and metabolic acidosis with increased anion gap, both common in hospitalized medical patients, can counteract the generally opposite relationship between serum chloride and bicarbonate concentrations seen in most metabolic and respiratory acid-base disorders.

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We performed a study on 135 hospitalized internal medicine patients with abnormal serum electrolyte concentrations to examine how often and to what extent water disturbances, manifested as hypo- or hypernatremia, and metabolic acidosis with increased anion gap alter relationships between serum chloride and bicarbonate concentrations in internal medicine inpatients. Our hypothesis was that once disturbances in serum sodium and anion gap were considered, there would be a nearly perfect inverse correlation between serum chloride and bicarbonate concentrations in these patients.

MATERIALS AND METHODS

Normal Controls

To obtain a normal control group for comparison with patients with electrolyte disorders (see below), we reviewed serum chemistry analyses in 1,087 consecutive adult patients (498 male and 589 female) whose blood had been sent to the laboratory for any reason. To be selected as a normal control, concentrations of each of the seven analytes listed in Table 1 had to be within our laboratory's published normal range. Reference ranges for the analytes listed in Table 1 were validated by utilizing the transference method outlined in the National Committee for Clinical Laboratory Standards (NCCLS; <http://www.nccls.org>) C28-A2 guidelines (6). Forty apparently healthy outpatients of mixed gender and age were used as reference range controls. One hundred thirty five of the 1,087 samples (12%) fulfilled these stringent criteria for normality. Table 1 shows the mean ($\pm$ SD) for each of the seven analytes in these 135 controls, as well as our laboratory's reference ranges. Upper and lower limits of normal were calculated from the mean values ($\pm$ 1.96 SDs of the means) and are also presented in Table 1; these values were used to

determine whether the 135 medical inpatients (described below) had low, normal, or high serum chloride and/or bicarbonate concentrations. We believed that we would gain some statistical power by using a larger group of normal controls ($n = 135$) rather than using the reference range controls ($n = 40$) when comparing controls with the patients with abnormal serum electrolytes.

Medical Patients With Abnormal Serum Electrolytes

We examined serum chemistry results at the time of admission in 135 medical patients (70 male, 65 female). Their ages ranged from 17–103 years (mean, 54). Each had been admitted to the general internal medicine teaching service at the Presbyterian Hospital of Dallas with a serum electrolyte abnormality (low or high sodium, low or high chloride, and/or low or high bicarbonate). Many also had a low or high serum potassium, but patients with isolated abnormalities in serum potassium were excluded. The vast majority of the patients were admitted to a general medical/surgical floor and only a few were admitted to an intensive care unit. Their admitting diagnoses are listed in Table 2.

Laboratory Technology

Serum samples were analyzed using a Vitros 950 autoanalyzer (Ortho Clinical Diagnostics, Raritan, NJ). This analyzer measures total CO_2 concentrations. However, we will refer to total CO_2 concentrations measured with this instrument as serum bicarbonate concentrations.

Statistical Methods

Data were imported from the clinical chemistry laboratory into spread sheets (Microsoft Excel 2002,

TABLE 1. Analytes in patients with all analytes within the normal reference ranges for our laboratory (normal controls) and in internal medicine patients*

Analyte	Controls ($n = 135$) Mean $\pm$ SD (LLN, ULN)	Patients ($n = 135$) Mean $\pm$ SD (range)	<i>P</i> value
Serum Na (mM)	140 $\pm$ 2 (135, 144)	135 $\pm$ 9 (102–153)	<0.0001
Serum K (mM)	4.2 $\pm$ 0.4 (3.5, 4.9)	4.3 $\pm$ 1.2 (2.0–7.8)	N.S.
Serum Cl (mM)	106 $\pm$ 2 (101, 111)	99 $\pm$ 11 (69–123)	<0.0001
Serum HCO_3^- (mM)	26 $\pm$ 2 (22, 30)	20 $\pm$ 8 (3–43)	<0.0001
Serum anion gap (mM) ^a	8 $\pm$ 2 (3, 12)	15 $\pm$ 8 (3–40)	<0.0001
Serum creatinine (mg/dL)	0.9 $\pm$ 0.2 (0.6, 1.3)	3.0 $\pm$ 3.5 (0.4–18.9)	<0.0001
Blood urea nitrogen (mg/dL)	13 $\pm$ 3 (6, 19)	40 $\pm$ 36 (5–162)	<0.0001
Blood glucose (mg/dL)	91 $\pm$ 10 (72, 111)	211 $\pm$ 241 (25–1,879)	<0.0001
Serum Cl/serum Na	0.76 $\pm$ 0.02 (0.73, 0.79)	0.74 $\pm$ 0.05 (0.57–0.86)	<0.0001
Serum HCO_3^- /serum Na	0.19 $\pm$ 0.01 (0.14, 0.21)	0.15 $\pm$ 0.06 (0.02–0.32)	<0.0001

*Reference ranges were as follows: Na, 135–145 mM; K, 3.5–5.0 mM; Cl, 97–109 mM; HCO_3^- , 19–28 mM; creatinine, 0.8–1.5 mg/dL; blood urea nitrogen, 9–20 mg/dL; blood glucose, 65–110 mg/dL.

^aSerum Na – (Cl + HCO_3^-).

LLN, lower limit of normal (mean minus 1.96 SD of the mean); ULN, upper limit of normal (mean plus 1.96 SD); N.S., not significant.

TABLE 2. Primary admitting diagnoses of 135 medical patients

Diagnosis	Patients
Acute or chronic renal failure	31
Diabetic ketoacidosis or hyperglycemic, hyperosmolar nonketotic state	16
Cirrhosis	10
Vomiting disorder	9
Congestive heart failure	8
Volume depletion (secondary to decreased oral intake or to diuretics)	8
Diarrhea	5
Pneumonia	5
Intestinal obstruction	4
Prescription drug toxicity ^a	4
Alcohol withdrawal syndrome	3
Syndrome of inappropriate ADH release	3
Acute hepatitis ^b	3
Septic shock	3
Endocrinologic disorder ^c	3
Cancer ^d	4
Alcohol intoxication	2
Bacterial endocarditis	2
Gastroenteritis	2
Submersion injury	2
Miscellaneous ^e	8

^aOne case each of these prescription drugs: combined aspirin/acetaminophen, carisoprodol, tricyclic antidepressant, and insulin.

^bOne case each of alcoholic, viral, and drug-induced hepatitis.

^cOne case each of hypothyroidism, congenital adrenal hyperplasia, and Cushing's disease.

^dOne case each of breast, pelvic, transitional cell kidney, and brain cancer.

^eOne case each of milk-alkali syndrome, Still's disease, malaria, eclampsia, PCP toxicity, cerebrovascular accident, hematuria on warfarin, and ureteroileostomy.

Microsoft Corp., Redmond, WA). Differences between groups were tested for significance by group *t*-tests, with *P* values <0.05 considered significant. Patients were classified into nine groups based upon whether their serum chloride and bicarbonate concentrations at the time of admission were low (L), normal (N), or high (H). After this classification, we adjusted serum chloride and bicarbonate, as follows:

$$\text{adjusted Cl} = \text{measured Cl} + 0.76(140 - \text{measured Na}) \quad (1)$$

$$\text{adjusted HCO}_3 = \text{measured HCO}_3 + \Delta \text{anion gap} + 0.19(140 - \text{measured Na}) \quad (2)$$

These formulas used the expected serum ratios of chloride to sodium of 0.76 ± 0.02 and bicarbonate to sodium of 0.19 ± 0.01 (Table 1). The Δ anion gap represents the difference between the patient's anion gap $[\text{Na} - (\text{Cl} + \text{HCO}_3)]$ and the mean anion gap in our normal

controls, which was 8 ± 2 mM (Table 1). Thus, Δ anion gap could be positive, negative, or zero.

RESULTS

Table 1 shows mean ($\pm$ SD) concentrations of the seven analytes in the 135 medical patients, as well as their wide ranges. With the exception of serum potassium, mean values in patients differed significantly from controls ($P < 0.0001$). Serum chloride ranged from 69–123 mM, bicarbonate from 3–43 mM, and sodium from 102–153 mM. An abnormal serum Na (low or high) was present in 73 patients (54%) and an increased anion gap was present in 76 patients (56%); 34 (25%) had both abnormalities.

Table 3 classifies the 135 patients by their serum sodium and anion gap category. Note that there were 42 patients (31%) with eunatremia and high anion gap and 35 other patients (26%) with hyponatremia with normal anion gap. The former 42 would be expected to frequently exhibit euchloremia with hypobicarbonatemia while the latter 35 would be expected to frequently exhibit dilutional hypochloremia with or without hypobicarbonatemia.

Table 4 shows the classification of the 135 patients based upon whether serum chloride and bicarbonate levels were low (L), normal (N), or high (H). Numbers of patients with each of the nine possible combinations (LL, LN, LH, NL, NN, NH, HL, HN, and HH) are shown on admission (before adjustment) and after adjustment for anion gap and serum sodium. Only 24 of the 135 patients (18%) retained the same serum chloride/bicarbonate classification after adjustment. For example, eight patients had a low serum chloride and high serum bicarbonate before and after adjustment (see LH, Table 4). The most common changes in classification after adjustments were a normal chloride/low bicarbonate (NL) reverting to a normal chloride/high bicarbonate (NH), occurring in 29 patients, and a low chloride/normal bicarbonate (LN) reverting to a normal chloride and bicarbonate (NN), occurring in 17 patients. Serum chloride and bicarbonate levels before adjustments were both abnormal in 41 patients, being concordant in 23 (LL) and discordant in 18 (LH in 9 and HL in 9). In contrast, serum chloride and bicarbonate levels after adjustment were both abnormal in 40 patients, and in each instance they were discordant (LH in 31 and HL in 9).

Thirty one patients on admission (31%) had an LN pattern, but this was largely due to hyponatremia, as only five retained the LN pattern after adjustments. Likewise, 51 patients (38%) had an NL pattern on admission. The majority of these 51 patients (29 or 76%) actually had a hidden metabolic alkalosis (NH pattern

after adjustments); 12 others reverted to a NN pattern and only three (2%) retained the NL pattern after adjustments.

After adjustments for anion gap and serum sodium, serum chloride ranged from 83–120 mM and serum bicarbonate ranged from 12–48 mM in these 135 patients. Moreover, there was a nearly perfect correlation between chloride and bicarbonate after adjustments for anion gap and serum sodium ($r = -0.998$; Fig. 1a). This contrasted with a modest inverse correlation between measured serum chloride and bicarbonate concentrations at the time of admission ($r = -0.459$; Fig. 1b). This modest correlation was mainly attributed to the water disturbances (hypo- and hypernatremia), as the correlation only improved slightly ($r = -0.586$) when anion gap-adjusted bicarbonate was correlated with the measured serum chloride (data not shown).

DISCUSSION

The concentration of sodium, the major cation in the extracellular compartment, normally exceeds the sum of the chloride and bicarbonate concentrations due to an excess of “unmeasured” anions, such as albumin,

phosphate, and lactate over “unmeasured” cations, such as potassium, calcium, and magnesium. If the serum sodium concentration remains constant (i.e., there is water balance) and if there are no unbalanced changes in the concentrations of these “unmeasured” anions and cations, the sum of the chloride and bicarbonate must remain constant. Under these circumstances an increase (or decrease) in the concentration of chloride ions should be accompanied by an equal and reciprocal decrease (or increase) in the concentration of bicarbonate ions to maintain electrical neutrality.

In the setting of free water disturbances, which were present in over half of our hospitalized internal medicine patients, the serum sodium, chloride, and bicarbonate concentrations move in the same direction, except when a competing acid-base disorder is present. The fall in serum chloride with a water excess (or the rise with a water deficit) should be close to three-fourths the fall (or rise) in serum sodium, as the ratio of serum Cl to Na in our normal controls was 0.76 ± 0.02 (Table 1). Likewise, the fall (or rise) in serum bicarbonate with a water excess (or deficit) should be close to one-fifth the fall (or rise) in sodium, as the ratio of HCO_3^- to Na in our normal controls was 0.19 ± 0.01 (Table 1). Thus, excesses or deficits in electrolyte free water influenced concentrations of the more plentiful chloride ion to a 4-fold greater extent than concentrations of the less plentiful bicarbonate ion, resulting in an imperfect inverse relation between the two anions when there is free water imbalance. Since correction factors may vary slightly from laboratory to laboratory, the 0.76 and 0.19 values we used for Cl/Na and HCO_3^-/Na , respectively, should be considered approximate, and it may behoove other laboratories to determine their own correction factors.

TABLE 3. Classification of 135 medical patients by their serum sodium and anion gap on admission

Serum sodium	Low anion gap	Normal anion gap	High anion gap	Total
Low	0	35	26	61
Normal	0	20	42	62
High	0	4	8	12
Total	0	59	76	135

TABLE 4. Classification of 135 medical patients based on serum chloride and bicarbonate concentrations after and before adjustment for serum anion gap and water imbalance*

After								
HN (n = 4)	—	—	—	3	—	—	1	—
HL (n = 9)	—	—	—	4	—	—	5	—
NH (n = 31)	—	—	—	29	2	—	—	—
NN (n = 44)	8	17	—	12	3	1	3	—
NL (n = 8)	1	—	—	3	2	—	—	2
LH (n = 31)	12	9	8	—	—	—	—	2
LN (n = 8)	2	5	1	—	—	—	—	—
Before →	LL (n = 23)	LN (n = 31)	LH (n = 9)	NL (n = 51)	NN (n = 7)	NH (n = 1)	HL (n = 9)	HN (n = 4)

*Adjustment to serum chloride by Eq. (3) and to serum bicarbonate by Eqs. (1) and (2) in text. No patient had HH and none had LL after adjustments.

LL, low chloride, low bicarbonate (see Table 1); LN, low chloride, normal bicarbonate; LH, low chloride, high bicarbonate; NL, normal chloride, low bicarbonate; NN, normal chloride, normal bicarbonate; NH, normal chloride, high bicarbonate; HL, high chloride, low bicarbonate; HN, high chloride, normal bicarbonate; HH, high chloride, high bicarbonate.

Fig. 1. Relationship between serum chloride concentration and serum bicarbonate (HCO_3^-) concentration in 135 medical patients, after and before adjustment for serum sodium and anion gap (see text). **a:** After adjustment, the correlation approached unity ($r = -0.998$, $P < 0.001$). **b:** Before adjustment, there was only a modest, but still significant inverse relationship between these parameters ($r = -0.459$, $P < 0.001$).

In our population, which was selected because they had abnormal serum electrolytes, deciding on admission whether their serum chloride and bicarbonate was low, normal, or high usually gave misleading information. This occurred because increases in the serum anion gap (due to accumulation of “unmeasured” anions), and decreases in serum sodium concentrations (due to hyperglycemia or excess antidiuretic hormone (ADH) activity), were common in this population. Less than one in five patients had the same chloride/bicarbonate combination after adjustments for serum sodium and anion gap that he or she exhibited on admission. This

varied considerably depending on the initial chloride-bicarbonate combination on admission. For example, virtually all people with a NL, LL, or HN pattern changed classification after adjustments, while most of those with an LH or HL pattern retained their pattern (Table 4).

Serum chloride and bicarbonate were equal and opposite indicators of acid-base disorders once free water excesses/deficits and unmeasured anions were considered (Fig. 1a). Clinicians and laboratory medicine specialists should be careful when interpreting low or high serum chloride or bicarbonate concentrations as

reflecting an acid-base disorder or when interpreting normal serum chloride and bicarbonate concentrations as not reflecting an acid-base disorder if hyponatremia or hypernatremia is present. We present a simple, practical, and reliable method of correcting serum chloride and bicarbonate when hyponatremia or hypernatremia is present.

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REFERENCES

1. Khanna A, Kurtzman NA. Metabolic alkalosis. *Respir Care* 2001;46:354–365.
2. Galla JH, Gifford JD, Luke RG, Rome L. Adaptations to chloride-depletion alkalosis. *Am J Physiol* 1991;262:R771–R781.
3. Sterns RH. Fluid, electrolyte, and acid-base disturbances. *J Am Soc Nephrol* 2003;2:1–33.
4. Foster GT, Vaziri ND, Sassoon CS. Respiratory alkalosis. *Respir Care* 2001;46:384–391.
5. Adroque HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998;338:26–34.