Base-excess chloride; the best approach to evaluating the effect of chloride on the acid- base status: a retrospective study

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Abstract

Background: To determine the effect of chloride on the acid-base status, four approaches are currently used: 1) accepted ranges of serum chloride values; 2) chloride corrections, such as chloride deficiency/excess and chloride modification; 3) the Cl/Na ratio; and 4) the sodium- chloride difference, such as base-excess chloride. However, these approaches are governed by different concepts, and they can evaluate the effects of chloride on the acid-base status differently. Our aim is to investigate which approach to the evaluation of the effect of chloride is the best.

Methods: In this retrospective cohort study, 2529 critically ill patients who were admitted to the tertiary care unit were evaluated between 2011 and 2018. Patient characteristics and blood gas parameters at the ICU admission and outcomes were recorded. The effects of chloride on the acid-base status according to each evaluative approach were validated by the standard base excess and apparent strong ion difference. To compare approaches, kappa and Bland-Altman tests and a linear regression model were used.

Results: In the linear regression model for all patients, only base-excess chloride in all the chloride evaluation approaches was significantly related to the standard base excess. In the subgroup, the correlation and limits of agreement between base-excess chloride and the standard base excess were the strongest (r2=0.92 p<0.001 bias: 0.5mmol/L).

Conclusions: For the evaluation of the effect of chloride on the acid-base status, base-excess chloride is a better approach than accepted ranges of serum chloride values, chloride corrections and the Cl/Na ratio.

Introduction

Chloride (Cl) is the major extracellular strong anion, and there is no suspicion that hyperchloremia and hypochloremia result in metabolic acidosis and alkalosis, respectively [1]. However, the definitions of normochloremia, hypochloremia and hyperchloremia are unclear. Currently, four approaches are used to detect the effect of Cl on the acid-base status: 1) the use of accepted range of serum Cl values; 2) chloride corrections, such as Cl deficiency/excess ($Cl_{def/exc}$) and Cl modification (Cl_{mod}); 3) the sodium (Na)-Cl difference, such as base-excess chloride (BE_{Cl}); and 4) the Cl/Na ratio [1–5]. However, each of these approaches has different fundamental concepts. Moreover, different normal limits for observed Cl (Cl_{obs}) can be accepted, such as 98–106 mmol/L, 100–108 mmol/L and 95–110 mmol/L [6–8]. On the other hand, for the same patient, Cl corrections, the Cl/Na ratio and BE_{Cl} can yield different effects of Cl on the acid-base status at the same time. These different results may lead to different diagnoses and treatments. Hence, the important question is which approach is the most accurate. Therefore, the aim of this study is to investigate which approach to the evaluation of the effect of Cl is the most reliable.

Methods

Study population

After receiving approval from the Acıbadem University Medical Research Assessment Council (ATADEK, 2016–18/1), 2529 patients who were admitted to the tertiary intensive care unit (ICU) in Acıbadem International Hospital were retrospectively evaluated between January 1st, 2011, and January 1st, 2018. Patients who were under 18 years old, readmitted or had missing blood gas parameters and outcomes were excluded (Fig. S1 in the Supplementary Appendix).

Database

Patient demographic and laboratory data were collected from the Acıbadem Health Group Database. ABL 800 (Radiometer, Denmark, Copenhagen), which employs an ion-selective electrode, was used for blood gas analysis. At ICU admission, demographic data (age, sex), diagnosis (medical, elective and emergency surgeries), Acute Physiology And Chronic Health

Evaluation II (APACHE II) score, pH, P_aCO_2 (mmHg), Na (mmol/L), K (mmol/L), Ca (mmol/L), Cl (mmol/L), HCO_3 (mmol/L), standard base excess (SBE) (mmol/L), apparent strong ion difference (SID_a) (mmol/L), effective strong ion difference (SID_e) (mmol/L), strong ion gap (SIG) (mmol/L), BE_{Cl} (mmol/L), serum lactate (mmol/L), albumin (g/L) and outcomes were recorded.

Normal values for Na and Cl (Na_n and Cl_n) and calculations

For the first approach that only Cl_{obs} levels are used, Cl_n ranges were accepted as 98–106 mmol/L [6]. For the $Cl_{def/exc}$, Na_n and Cl_n were 142 mmol/L and 104–108 mmol/L respectively whereas they were 140 mmol/L and 102 mmol/L for the Cl_{mod}. While there are no Na_n and Cl_n for the BE_{Cl} and Cl/Na ratio, normal values of BE_{Cl} and Cl/Na ratio were zero and 0.75–0.80 respectively[2–4,6]. All formulations and evaluations are detailed for all Cl approaches in Table 1.

SID_a, SID_e, SIG, $Cl_{def/exc}$, Cl_{mod} and BE_{Cl} were calculated as follows:[9]

$SID_a = (Na + K + Ca) — (Cl + lactate)$

$SID_e = (2.46 \times 10^{-8} \times (P_aCO_2/10^{-pH})) + (albumin\ in\ g/L \times (0.123 \times pH — 0.631)$

$SIG = SID_a - SID_e$

$Cl_{def/exc} = Cl_n - (Cl_{obs} \times (Na_n / Na_{obs}))$, $[Na_n = 142, Cl_n = 104–108]$

$Cl_{mod} = Cl_n - (Cl_{obs} \times (Na_n / Na_{obs}))$, $[Na_n = 140, Cl_n = 102]$

$BE_{Cl} = (Na_{obs} - Cl_{obs} - 32\ mmol/L)$

To detect only the effect of Cl on the acid-base status, a subgroup that included patients with normal lactate (≤1.6 mmol/L), albumin (≥35 gl/L, the lowest value of normal laboratory limits) and SIG (0–2 mmol/L) values was created [3,9].

Statistical analysis

All data were analysed by using SPSS version 26. The Kolmogorov-Smirnov test was used to detect normal distributions. The data were presented as percentages or medians (minimum-maximum). The effects of chloride on the acid-base status according to the different approaches were validated by the SBE and SID_a. The agreement between each pair of approaches was analysed with the Kappa test. The Pearson correlation was used for all correlations. For all patients, Cl_{obs}, $Cl_{def/exc}$, Cl_{mod}, Na_{obs}, Cl/Na ratio, K, Ca, BE_{Cl}, albumin, lactate, SIG and P_aCO_2 were added to the multivariate linear regression models to determine their relationship with the SBE. In the subgroup, the Bland & Altman test was used to determine the limits of agreement between SBE and each of Cl_{mod}, $Cl_{def/exc}$ and BE_{Cl}. Acceptable agreement was a bias of up to ±1 mmol/L and the limits of agreement were less than ±1.96 mmol/L. A p-value <0.05 was considered statistically significant.

Results

Two thousand two hundred seventy-two patients were included in this study (Supplementary material Fig. S1). The median values of SBE, BE_{Cl}, $Cl_{def/exc}$, Cl_{mod} and the Cl/Na ratio were −1.0, −1.0, −1.5, −6.0 and 0.77 in all patients, respectively (Table 2). In both the entire cohort and the subgroup, correlations among BE_{Cl}, SID_a and SBE were stronger than those for other approaches ($r^2 = 0.89$ $r^2 = 0.95$ and $r^2 = 0.92$, respectively) (Table 3). All measures of agreement between the approaches were weak (kappa<0.50) (Supplementary material Table S1). Only BE_{Cl} had acceptable limits of agreement with SBE in the subgroup (bias: 0.5 mmol/L) (Fig 1). In the linear regression models for all patients, $PaCO_2$, BE_{Cl},K, Ca, lactate, albumin and

SIG were significantly related to SBE ($p<0.001$ for all) whereas Na_{obs}, Cl_{obs}, Cl/Na ratio, $Cl_{def/exc}$ and $Cl_{mod,}$ were not. Additionally, every 1 mmol/L increase in BE_{Cl} was associated with a 0.90 mmol/L increase in the SBE ($p<0.001$) (Table 4).

Discussion

Definitions of hyperchloremic acidosis and hypochloremic alkalosis

Siggaard-Andersen emphasized that the degree of acidity was related to the amount of H^+ ions after Arrhenius developed the dissociation theory [10]. Stewart and Kellum also mention that the unlimited source of H^+ ions is water in the body [11,12]. Under these circumstances, the amount of H^+ ions in the plasma should be determined by water dissociation. However, terminologically, the use of hyperchloremia and hypochloremia to define Cl effect on acid-base status appears that only Cl level changes cause water dissociation and vice versa. Yet, the Stewart approach defines 3 independent variables to determine H^+ ions in the plasma, one of which is SID_a [2,10,12]. In other words, the difference between strong cations and anions determines whether water will dissociate. Since the major cations and anions are Na and Cl in the plasma, water dissociation should depend on the Na-Cl difference, not only the Cl level. Already, Story et al. showed that hyperchloremic acidosis was a type of SID_a acidosis [13,14]. Therefore, if Tani et al. had defined their groups in accordance with SID_a values instead of only Cl levels, they would not have made the mistake that they did, with the mean SID_a value of their normochloremia group as low as 33.9±3.5 [6,7]. Hence, we think that using accepted Cl limits to define hyperchloremic acidosis or hypochloremic alkalosis is not adequate. Our study clearly showed that using only accepted Cl limits gave us different results when compared to other approaches. It had the weakest correlations and Cl_{obs} was not associated with the SBE (Tables 1, 3 and 4). We believe that the reason for incompatible results in some chloride studies may be the use of the accepted Cl limits [6,7,15].

Chloride corrections and the Cl/Na ratio vs BE_{Cl}

The other approaches to evaluating the effect of Cl on the acid-base status are chloride corrections, the Cl/Na ratio and BE_{Cl} [2–5]. Since each of them is supposedly based on the Stewart approach, each should correlate with SID_a. In this study, we found that there were correlations between SID_a and each approach in the whole cohort and the subgroup (Table 3). However, the correlation of BE_{Cl} was stronger than those of $Cl_{def/exc}$, Cl_{mod} and the Cl/Na ratio. Furthermore, there was limited agreement among them, and we obtained different results for a single patient by using each of the approaches at the same time (Table 1 and Supplementary material Table S1). We think that there may be several explanations of these results. First, the corrections states that Cl_{obs} should be corrected in accordance with Na because Na and Cl should be similarly diluted or concentrated based on the gain or loss of water [2]. This thesis may be valid in vitro. However, it is known that the distributions of Na and Cl among compartments in the body differ because of the Gibbs-Donnan effect, Hamburger shift, absorption mechanisms in the kidney and small and large intestines and the effects of some drugs, such as furosemide [1,16–18]. Therefore, the Na and Cl concentrations may not increase or decrease in the same manner in different clinical situations. In fact, even if Na and Cl are similarly diluted or concentrated, the corresponding acidosis or alkalosis cannot be explained because SID will be constant. Furthermore, in the classification by Fencl, it is a paradox to use only Na levels to evaluate water excess or deficit while claiming that the dilution or concentration of Cl and Na are the same [2]. Second, the corrections are actually based on the Cl/Na ratio (Table 1) [2,3]. The Cl/Na ratio is another usable parameter because it is based on the Na_{obs} and Cl_{obs} levels. Thus, Cl/Na ratio studies have consistent results as well [5,19,20]. However, in addition to using the Cl/Na ratio, correction approaches create a fictitious Cl level by using the accepted normal value ranges for Cl and Na. Yet, it does not make sense to correct Cl when an Cl_{obs} level exists. The Stewart approach mentions neither the ratio nor normal value ranges [11,12]. The only rule in this concept is the difference between strong cations and anions, which almost equals the Na-Cl difference defined as BE_{Cl} by O'Dell et al. [4,12]. For this reason, BE_{Cl} should be the most valuable parameter for the evaluation of the effect of Cl. In this study, we found two more important pieces of evidence supporting the superiority of BE_{Cl}: a) the bias between BE_{Cl} and SBE in the subgroup that had normal metabolic values except Cl was less than that of the

correction approach (Fig. 1), and b) BE_{Cl} was significantly related to the SBE in all patients, whereas the correction and Cl/Na ratio approaches were not (Table 4). In other words, BE_{Cl} wasthe only parameter which determines Cl effect on SBE.

Additionally, these results compel us to think on two important issues: a) whether there are normal value ranges for Na and Cl or not. Although normal values of Na and Cl for physiologic events in the body exist, it appears that they are irrelevant while evaluating the acid-base status if BE_{Cl} is the most reliable approach to evaluate Cl effect. b) the relationship between $PaCO_2$ and SBE. This relationship is an evidence that $PaCO_2$,which is accepted as a determinant for respiratory acid-base disturbances, is actually a metabolic end-product and one of the components of SBE.

Conclusions

A chloride evaluation approach should conform with the electroneutrality law and, consequently, the Stewart approach. According to our results, the best chloride evaluation approach that meets these conditions is BE_{Cl}. Hence, the normal value ranges for Na and Cl should be questioned. We believe that this point of view will change the perspective on acid-base evaluation and fluid management.

Abbreviations

APACHE II : Acute Physiology And Chronic Health Evaluation II

BE_{Cl} : base excess chloride

Cl_n : normal chloride

Cl_{obs} : observed chloride

$Cl_{def/exc}$: chloride deficiency/excess

Cl_{mod} : chloride modification

Na_n : normal sodium

Na_{obs} : observed sodium

SBE : standard base excess

SID_a : apparent strong ion difference

SID_e : effective strong ion difference

SIG : strong ion gap

Declarations

Ethics approval and consent to participate

The study were approved by the Acıbadem University Medical Research Assessment Council (ATADEK, 2016-18/1).

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Contributions

BG, KG and US analyzed and interpreted the data. BG, FT and HKA were responsible for the data collection. BG wrote the article and LT was the major contributors in writing the manuscript. The authors read and approved the final manuscript.

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Tables

Table 1. Distribution of hypo, hyper and normo-chloremic patients in accordance with different chloride approaches

		Formulations	Accepted normal values for Na and Cl	Evaluations	Hypo chloremia n (%)	Normo chloremia n (%)	Hyper chloremia n (%)	Total n
Traditional approach	Cl_{obs}[6]	-	98≤ Cl_{obs} ≤106	Hypo; Cl_{obs}<98 Normo; 98≤Cl_{obs}≤106 Hyper; Cl_{obs}>106	196 (8.6)	1063 (46.8)	1013 (44.6)	2272
Chloride corrections	$Cl_{def/exc}$[2]		104 ≤ Cl_{corr} ≤108 Na_n = 142	Hypo; $Cl_{def/exc}$>0 (104 - Cl_{corr}) Normo; $Cl_{def/exc}$=0 (104≤Cl_{corr}≤108) Hyper; $Cl_{def/exc}$<0 (108 - Cl_{corr})	301 (13.2)	538 (23.7)	1433 (63.1)	2272
	Cl_{mod}[3]		Cl_n = 102 Na_n = 140	Hypo; Cl_{mod}>0 (102 - Cl_{corr}) Normo; Cl_{mod}=0 (Cl_{corr}=102) Hyper; Cl_{mod}<0 (102 - Cl_{corr})	263 (11.6)	1 (0.0004)	2008 (88.4)	2272
Cl/Na Ratio	Cl/Na[5]		-	Hypo; Cl/Na<0.75 Normo; 0.75≤Cl/Na<0.80 Hyper; Cl/Na≥0.80	488 (21.5)	1247 (54.9)	537 (23.6)	2272
Na-Cl difference	BE_{Cl}[4]		-	Hypo; BE_{Cl}>0 Normo; BE_{Cl}=0 Hyper; BE_{Cl}<0	885 (39.0)	210 (9.2)	1177 (51.8)	2272

BE_{Cl}, base excess-chloride; Cl_{corr}, corrected chloride; $Cl_{def/exc}$, chloride deficiency-excess; Cl_{mod}, chloride modification; Cl_n, normal chloride level; Cl_{obs}, observed serum chloride level; Na_n, normal Na level; Na_{obs}, observed serum Na level; [#], corrected chloride equations.

Table 2. Characteristics and outcomes for all patients and subgroup

	All patients (n=2272)	Subgroup (n=168)
Age, year	62 (18 – 98)	61.5 (18 – 97)
Male, n, %	1279 (56.3)	86 (51.2)
APACHE II,	12 (0 – 47)	11 (0 – 24)
Diagnosis, n, %		
Medical	1346 (59.2)	106 (63.1)
Elective surgery	803 (35.3)	58 (34.5)
Emergency surgery	123 (5.5)	4 (2.4)
pH,	7.39 (6.74 – 7.72)	7.40 (7.28 – 7.64)
P_aCO_2, mmHg	38.6 (7.5 – 145)	39.2 (19.8 – 52)
HCO_3^-, mmol/L	23.3 (4 – 51)	24.1 (18.4 – 33.1)
SID_a, mmol/L	34.8 (7 – 72)	35.5 (28.3 – 45.5)
SIG, mmol/L	2.2 (-43.4 ; 41.4)	0.95 (0.03 – 1.98)
SBE, mmol/L	-1.0 (-27.7 ; 23.1)	-0.1 (-6.9 ; 8.8)
BE_{Cl}, mmol/L	-1.0 (-23.0 ; 37.0)	-1.0 (-6.0 ; 8.0)
$Cl_{def/exc}$, mmol/L	-1.5 (-23.4 ; 24.8)	-1.8 (-7.1 ; 3.2)
Cl_{mod}, mmol/L	-6.0 (-23.9 ; 51.5)	-6.2 (-11.4 ; 2.6)
Cl/Na ratio	0.77 (0.56 – 0.93)	0.77 (0.71 – 0.81)
Na, mmol/L	137 (98 – 177)	136 (128 – 144)
Cl, mmol/L	106 (55 – 147)	105.5 (93 – 113)
K, mmol/L	4.0 (1.9 – 7.7)	4.0 (2.9 – 6.0)
Ca, mmol/L	1.12 (0.56 – 2.04)	1.11 (0.84 – 1.23)
Albumin, g/L	29 (10 – 49)	38 (36 – 42)
$Lactate^-$, mmol/L	1.4 (0.1 – 27)	0.9 (0.5 – 1.6)
Length of ICU stay, day	2 (1 – 160)	1 (1 – 18)
Mortality, n %	297 (13.1)	14 (8.3)

APACHE II, Acute Physiology and Chronic Health Evaluation; BE_{Cl}, base excess chloride; $Cl_{def/exc}$, chloride deficiency/excess; Cl_{mod}, chloride modification; ICU, intensive care unit; SBE, standard base excess; SID_a, apparent strong ion difference; SIG, strong ion gap.

Results were given percentage and median (min-max)

Table 3. Correlations in all patients and subgroup (r^2 values)

	In all patients (n=2272)		In subgroup (n=168)	
	SID_a	SBE	SID_a	SBE
Cl_{obs}	0.31	0.14	0.51	0.47
$Cl_{def/exc}$	0.81	0.24	0.83	0.81
Cl_{mod}	0.85	0.25	0.91	0.86
Cl/Na ratio	0.85	0.25	0.91	0.86
BE_{Cl}	0.89	0.24	0.95	0.92

BE_{Cl}, base excess chloride; $Cl_{def/exc}$, chloride deficiency/excess; Cl_{mod}, chloride modification; Cl_{obs}, observed serum chloride level; SBE, standard base excess; SID_a, apparent strong ion difference;

Table 4. Multivariate linear regression model for SBE (for all patients)

	Coefficient (CI 95%)	p
Cl/Na ratio	7.0 (-34.5 ; 48.4)	0.743
$Cl_{def/exc}$, (mmol/L)	-0.08 (-0.21 ; 0.04)	0.173
Cl_{obs}, (mmol/L)	-0.06 (-0.13 ; 0.01)	0.085
$PaCO_2$ (mmHg)	-0.08 (-0.09 ; -0.07)	***<0.001***
BE_{Cl}, (mmol/L)	0.90 (0.68 ; 1.11)	***<0.001***
K, (mmol/L)	0.50 (0.27 ; 0.65)	***<0.001***
Ca, (mmol/L)	0.60 (0.46 ; 0.73)	***<0.001***
Lactate, (mmol/L)	-1.23 (-1.28 ; -1.17)	***<0.001***
Albumin, (g/L)	-0.20 (-0.22 ; -0.17)	***<0.001***
SIG, (mmol/L)	-0.70 (-0.73 ; -0.67)	***<0.001***

Adjusted R^2: 0.74 Durbin Watson:1.89

BE_{Cl}, base excess-chloride; P_aCO_2, arterial carbon dioxide pressure; SIG, strong ion gap.

P_aCO_2, Na_{obs}, Cl_{obs}, Cl/Na ratio, Cl_{mod}, $Cl_{def/exc}$, BE_{Cl}, K, Ca, Albumin, lactate and SIG were included to the model using enter method. Na_{obs}, Cl_{mod}, were excluded by model because of their F values and correlations.

Figures

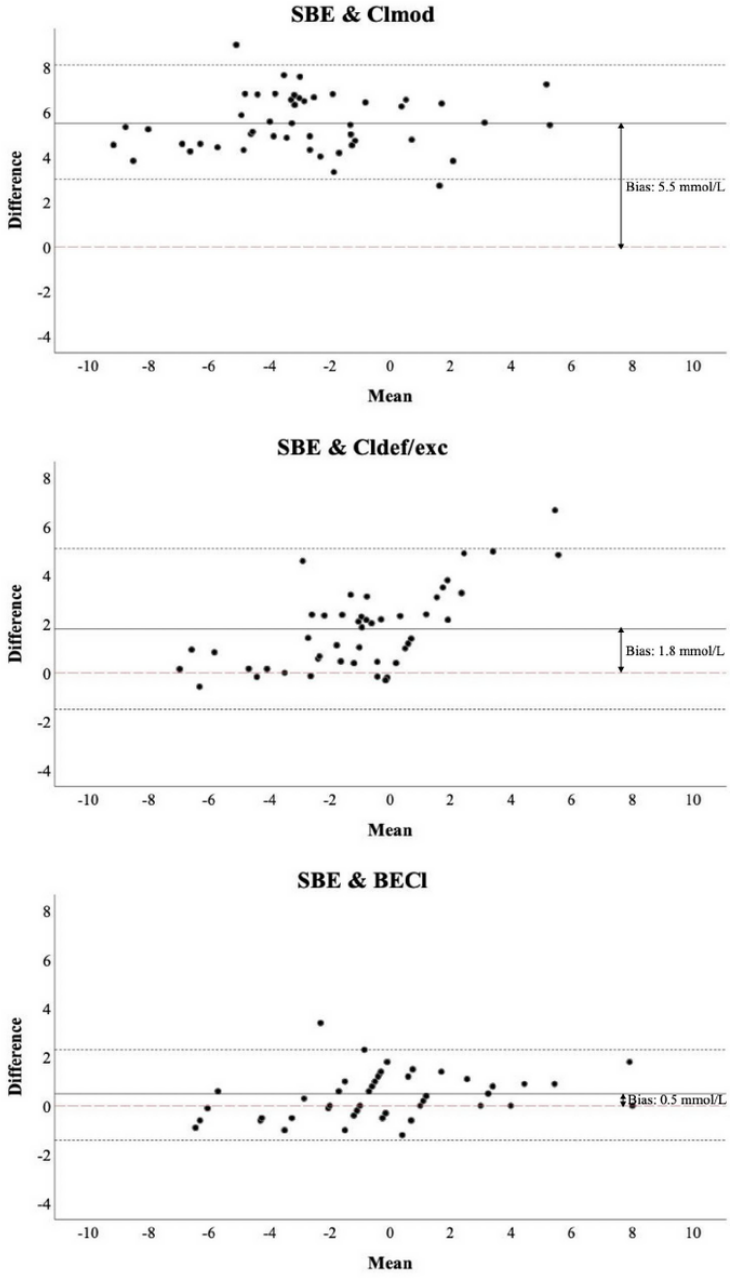

Figure 1

Limits of agreements (in subgroup)

Supplementary Files

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