Calculation of plasma chloride levels using blood gas measurements

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Abstract
Objective: Chloride is the major plasma anion. There are several methods available for the determination of serum chloride levels. Unfortunately these methods are sometimes not available in the urgent setting where values are needed. Here we describe a formula for estimating plasma chloride levels.
Methods: Fifty-two consecutive patients were enrolled for which serum chloride levels were estimated using the formula $CL^- = (Na^+ + 10 - TBB)$, and also measured directly through the colorimetric method. Correlation between the two values was analyzed using Pearson correlation coefficient and agreement was shown in the Bland-Altman plot.
Results: Comparing the values achieved through estimation and laboratory determination of plasma chloride revealed a significant correlation ($r = 0.97$). Consistent agreement was described within -4.8 and +6.6 on the Bland-Altman plot throughout the measurements.
Conclusion: The formula presented here may be a reliable alternative to direct measurement of serum chloride when direct results are not available
Keywords: Arterial blood gas (ABG), Total buffer base (TBB), Anion gap (AG), Serum chloride

Introduction

Chloride is the most important anion associated with sodium in the extra cellular fluid with a normal concentration ranging from 96 to 106 (1). The complete interpretation of acid-base disorders is impossible without knowing the serum chloride concentration (2). In the process of quantitative acid-base analysis, plasma pH is determined by three independent variables: pCO_2, total concentration of nonvolatile weak acids, and the strong ion difference (SID). On the other hand, bicarbonate (HCO_3) concentration is considered to be dependent on the SID. It has been suggested that chloride is the major electrolyte determining the SID and thus directly affecting acid-base disorders in the clinical setting (3). Furthermore, the serum chloride level has been associated with rates of mortality in certain groups of patients and has been suggested as a prognostic factor (4,5). Therefore, timely and accurate determination of serum chloride concentration is of great importance for decision-making in the emergency department. Several methods have been described for the measurement of serum chloride (6). The coulometric titration method uses electrolysis current to measure ion formation (7), while the ion-selective electrode uses a transducer to convert the activity of the chloride ion into an electrical potential, which can be measured by a voltmeter or pH meter (8).

The colorimetric method combines chloride with other elements to form a colored solution and then measures color density to determine chloride concentration (9). A cyclic voltammetry using an Ag electrode has also been described for selective measurement of chloride ions (10). These methods have been described for years and range in their complexity, cost, and accuracy, yet even today measurement of serum chloride levels is not available in Iranian hospitals as an emergent test 24 hours a day. To overcome this problem here we describe a formula for calculation of serum chloride levels using information available in the emergency setting through analysis of blood gases.

Methods

In this study the authors developed a practical formula based on known acid-base physiology. Then we predicted Cl^- concentration in 52 consecutive patients in the emergency department for which Cl^- concentration had been ordered by the treating physician. For each patient, three simultaneous samples were collected: One complete blood count tube, one clot sample for serum collection, and one arterial blood gas analysis heparinated sample. Serum Hb, electrolytes and blood gas analysis were derived from these samples. The results derived from the formula were compared with the biochemical report of the chlorine

sample from the laboratory. Correlation was analyzed using the Pearson coefficient and agreement described in the Bland-Altman plot.

The Stewart physicochemical approach to acid-base interpretation takes into account all the cations and anions that play a role in plasma electroneutrality (11). The plasma remains electrically neutral in physiologic and pathologic conditions through the equilibration of total cations with total anions. The concept is summarized in the formula below in which A- represents serum albumin, phosphorus, and other negatively charged proteins:

Strong ion difference (mmol/L) = [Na$^+$] + [K$^+$] + [Ca^{2+}]+[Mg^{2+}] – [Cl$^-$]

[Strong ion difference] – [A$^-$] = [HC$_{O3}^-$] + [CO$_3^{-2}$] + [(OH$^-$)] – [H$^+$]

The equation for SID – [A$^-$] can be reduced to approximately [HCO3–] because [HCO$_3^-$] is much greater than [H$^+$], [OH$^-$], and [CO$_3^{-2}$]. In addition, if one replaces the normal values for these concentrations in a physiologic state as shown in Table 1, several conclusions can be made: Since variations in K$^+$, Ca^{+2} and Mg^{+2} concentrations are trivial and their influence in the formula adds up to a total of approximately 10 meq/L we replace them with this value. Also we refer to the accumulative concentration of (Co$_3$H$^-$ + Po$_4$H^{-2} +Alb +Hb + others) as total buffer base (TBB). Then the following formula can be rewritten:

(Na$^+$ +10) = (Cl$^-$ +TBB) and finally

Cl$^-$ = (Na$^+$+10)-TBB

Box 1 summarizes these formulas.

Chloride was measured in a simultaneously collected serum sample. Care was taken for the serum to be extracted immediately after sample collection to limit alterations caused by cell metabolism. An automated colorimetric method was used. Chlorine was measured using colorimetric method by Randex kit, UK with Cl- 5526 ×100 mc, Reagent G×100 mc 2STd 11×5 mg 3ST, 1×5 mg. The chemical reaction led to the creation of ferric thiocyanate, a brown colored complex. The mixture was left to sit at

37°C for 270 seconds. The density of this substance was then measured using spectrophotometry at 505 nm wavelength compared to a standard sample which revealed the concentration of chloride. Although relatively simple, when available, the test was usually reported over 2-hours after sample collection in the emergency setting.

For practical purposes we chose a sample size according to the following formula:

$$N = \frac{(z_1 + z_2)^2 (6_1^2 + 6_2^2)}{d^2} = 48$$

which a =0.05, d=3 , 6$_1$ = 4, and 6$_2$=4.

Fifty-two sequential patients were enrolled, 33 male and 19 female. There was no limitation on the condition for which the test was ordered. In our study, patients suffered from varying disorders such as diabetic ketoacidosis, acute renal failure, chronic kidney disease, intoxication, gastroenteritis, suspected electrolyte or acid-base disturbances.

Results

Overall 52 patients were included in the study. For every case two chloride values were available: one through calculation and the other through direct biochemical measurement using the automated colorimetric method. Figure 1 shows the agreement between these two methods using the Bland-Altman plot. This diagram plots the difference between the values achieved through the formula and laboratory to the average of these two values and demonstrates the proximity of the two methods throughout the range of measurements obtained. Furthermore, Pearson coefficient was used to measure the statistical correlation between the two values and a correlation coefficient of r = 0.94 was reached, indicating excellent correlation of the two methods.

Discussion

Chloride is an important extracellular anion with proven impact on the acid-base status of the body (1-3). Although the best method for determining Cl- concentration is through direct measurement, sometimes this is not an option in the emergency setting. Here we have described a formula which predicts serum Cl- levels with strong cor-

Table 1. Normal values of serum electrolytes

Na$^+$ 142 meq/L	Cl$^-$ 103 meq/L
K$^+$ 4.3 meq/L	Co3H$^-$ 25 meq/L
Ca^{++} 4 meq/L	Po$_4$ H$^-$2 meq/L
Mg^{++} 2 meq/L	Proteins 16 meq/L Others (So$_4$H$^-$, Lactate) 6 meq/L
Total: 152 meq/L	Total: 152 meq/L

Box 1. Formula summary

Na+K+Ca+Mg=Cl+CO3+Protein+Hb+PO4
K+Ca+Mg=Unmeasurable cation ≈10 mmol
Protein+Hb+PO4 = Unmeasurable anion
HCO3+Protein+Hb+PO4 =TBB
Na+10 = Cl+TBB
CL= Na+10-TBB
Anion gap=UA-UC=Na-(Cl+CO3)
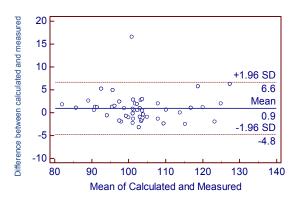Anion gap=UA-UC=Na-(Na+10-TBB+CO3)
Aniongap=TBB-(CO3+10)

Figure 1. Blad-Altman plot showing agreement between calculated and measured serum chloride levels

relation with the colorimetric method used as the reference value. There are several methods available for measurement of chloride levels in the laboratory including the autoanalyzer (colorimetric method), a coulometric method, a mercurimetric method, and a chloride-specific ion electrode method (1). Among these, the colorimetric method is considered to be simpler (12) and can be performed using automated apparatus. Here we used the colorimetric method as the reference value since this was the method available at our center. Unfortunately despite the importance of chloride concentration determination, this test is not available during off hours at our center and the use of an alternative formula for this purpose is welcomed. This is not the first time calculated formulas are turned to in hope of replacing direct measurement of plasma concentrations. Rees et al have described a computerized formula in order to estimate arterial O2 pressures using the data gained through venous sample blood gas analysis (13). Another example of using formulas to estimate values that are difficult to obtain is the estimation of glomerular filtration rate (14,15). These formulas help make quick decisions when waiting for a direct result is not an option. Chloride measurement is essential not only for etiologic evaluation of the acid-base status, but also for classification of the condition and choosing an often urgent path for treatment (i.e., saline-responsive or saline-resistant metabolic alkalosis or normal and high anion gap [AG] metabolic acidosis) (2,11). Therefore, in instances when the direct measurement of chloride is not performed urgently, our formula is a well correlated alternative which may help guide urgent management of patients. As seen on the Bland-Altman plot, almost all of the cases included in this study are plotted within a limited range of difference between negative and positive 5 mg/dL of one another. This means that the measurements usually differed less than 5 mg/dL which is considered acceptable in the clinical setting. Moreover, this agreement is consistent throughout the range of measurements made with no increased tendency towards bias at either end of the plot. The impressive Pearson coefficient further emphasizes the correlation between the values obtained from both methods. Our formula may further be developed to estimate the AG when Chloride levels are not available. For this purpose for AG we have:

$AG = Na^+ - (Cl^- + Co_3H^-)$

After substitution for chloride we have:

$AG = Na^+ - (Na^+ + 10 - TBB + Co_3H^-)$ or

$AG = TBB - (Co_3H^- + 10$

Through the same steps the Δ/Δ ratio can also be obtainable as follows: Δ/Δ Ratio $= (AG - 12) / (25 - Co_3H^-)$ or

Δ/Δ Ratio $= [TBB - (Co_3H^- + 22)] / (25 - Co_3H^-)$

Conclusion

The formulas presented in this paper are an accurate and acceptable alternative to direct measurement of serum chloride level in situations when direct analysis is not available.

Limitations

Limitations are an inherent part of clinical research. In our study we recognize that a larger patient sample could allow us to test the accuracy of our formula in a wider range of clinical settings and chloride levels. Also, due to the limited number of patients included and the variety of conditions for which serum chloride level measurement is desired, stratification of patients based on underlying condition was not an option. Larger studies may be able to test the accuracy of the formula in different settings such as toxicology, shock, respiratory disorders, etc. Lastly, in our study we used the colorimetric method as the reference value for serum chloride levels. This was due to the lack of availability of other measurement methods at our hospital. A comparison with the results obtained through different methods of measurement would have been more desirable.

Ethical issues

There were no ethical concerns since no extra blood was drawn from the patients and all interventions were based on the measured rather than the calculated chlorine concentration.

Authors' contributions

RH contributed to concept development, data gathering, and statistical analysis of the data. AM contributed to concept development and data gathering. AT contributed to statistical analysis and manuscript preparation of the paper.

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