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SHORT COMMUNICATION

BASE EXCESS SIGNIFICANTLY CORRECTED FOR THE VARIATIONS IN APPARENT DISSOCIATION CONSTANT FOR HUMAN BLOOD GAS TESTING

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Abstract : We introduce a pragmatic approach towards the corrected Base Excess (BE) by including the large variability of the apparent dissociation constant pK' in non-logarithmic form in Henderson-Hasselbach bicarbonate ion equilibria thereby resulting in a significant correction both in calculated bicarbonate ion concentration and BE at 37°C.

Key words : albumin, base excess, bicarbonate, blood gases, dissociation constant, pH

INTRODUCTION

Siggaard-Anderson and others have developed the standard (base excess) model of acid-base balance in common use today (1). This model has enjoyed much success as is used widely. The model is relatively easy to understand, based on experimental correlations, and relies on easy-to-measure variables. Others have criticized base excess (BE) for merely quantifying rather than truly explaining acid-base disturbances. The BE (or Base Deficit (BD) when BE is negative) is based on experimental correlations with curve fitting equation which was named as Van Slyke equation by Siggaard-Andersen (2).

At the heart of the BE model is the calculation of bicarbonate concentration utilizing the Henderson-Hasselbach equation (3). Both the solubility coefficient and the apparent first dissociation constant still vary even when temperature is fixed at 37°C. The solubility coefficient variation with interdependent variables e.g. ionic strength, pH, albumin concentration, etc. is rather small and thus ignored. On the other hand, small variations in the value of the apparent first dissociation constant gives rise to very large variations in bicarbonate concentration calculations of up to 60% (4). Further, pK' values less than 6.1 as well as greater than 6.3 for pediatric patients are not uncommon (5) resulting up to 170% in bicarbonate

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concentrations and hence also result in large variations in the value of BE. The blood gas testing equipment manufacturers have utilized a constant value of 6.1 for the apparent first dissociation constant. We offer three solutions to this problem, firstly, fast and accurate direct bicarbonate concentration measurement to obtain BE, secondly, an experimental solution involving additional measurement of ionic strength, albumin, ketones and lactates where warranted and thus added cost and utilizing it to obtain the corresponding more accurate value of the apparent first dissociation constant to obtain BE or thirdly, a pragmatic technological solution which includes the variability of the apparent first dissociation constant as a function of BE.

Hasselbach and Gammeltoft (6) and Hasselbach (3) adopted the Sorenson convention (where $[H^+]$ is expressed by pH), and presented the well-known "the Henderson-Hasselbach equation" as :

$$pH = pK' + \log [HCO_3^-]/(Sco_2 . Pco_2) \quad \text{(Eq. 1)}$$

where the total CO_2 concentration is expressed as $[CO_2] = Sco_2 * Pco_2$ where Sco_2 (the solubility coefficient of CO_2 in plasma, Henry's law) and Pco_2 (the partial pressure of CO_2 in plasma). Equation 1 can also be expressed as in non-logarithmic form with $K_1' = Sco_2 * 10^{-pK'}$ as :

$$[H^+] = K_1' . Pco_2/[HCO_3^-] \quad \text{(Eq. 2)}$$

The effect of pK' variability on $[HCO_3^-]$ calculation utilizing equation 1 when pK' is varied from 5.9 to 6.4 for both fixed pH = 7.4 and Pco_2 = 40 mmHg is shown in Table I. Note the large variation of the $[HCO_3^-]$ for very small variations in pK'. The logarithmic function hides the variations and $[HCO_3^-]$ calculations requires anti-log and brings forth the large variation in the $[HCO_3^-]$. Further equation 1 appears to break down at physiologic extremes. For example, the buffer curve, equation 1 indicates that the plot of log Pco_2 vs. pH should be linear with an intercept equal to –1 (7). However, experimental data cannot be fitted to the equation 1. The plot of pH vs. Pco_2 is in fact displaced by changes in protein concentration or the addition of sodium or chloride and becomes nonlinear in markedly acid plasma (7).

TABLE I: Variation of $[HCO_3^-]$, BE (equation 11) when pK' is varied from 5.9 to 6.4 for both fixed pH = 7.4 and Pco_2 = 40 mmHg.

pK'	*$[HCO_3^-]$*	*BE*
5.9	38.83	13.4
6.0	30.85	5.99
6.1	24.50	0.09
6.2	19.46	–4.59
6.2	15.46	–8.3
6.4	12.28	–11.26

METHODS

One approach is to use Sco_2 and pK' values for mammalian fluids which are dependent on ionic strength, protein concentration, etc. in computing $[HCO_3^-]$ from equation 1 but this involves costly and accurate measurement of ionic strength, protein concentration, etc. for pK' at 37°C. As an alternative Heisler (8, 9) developed complex equations for Sco_2 (mmol 1-1 mmHg-1) (1 mmHg = 133.22 Pa) and pK' that are purported to be generally applicable

to aqueous solutions (including body fluids) between 0° and 40°C and incorporate the molarity of dissolved species (Md), solution pH, temperature (T, °C), sodium concentration ([Na^+], mol 1-1), ionic strength of non-protein ions (I, mol 1-1) and protein concentration ([Pr], g 1-1):

$Sco_2 = 0.1008 - 2.980 \times 10^{-2}\,Md + (1.218 \times 10^{-3}\,Md - 3.639 \times 10^{-3})T - (1.957 \times 10^{-5}\,Md - 6.959 \times 10^{-5})T2 + (7.171 \times 10^{-8}\,Md - 5.596 \times 10^{-7})T3.$ (Eq. 3)

$pK' = 6.583 - 1.341 \times 10^{-2}\,T + 2.282 \times 10^{-4}\,T2 - 1.516 \times 10^{-6}\,T3 - 0.341I0.323 - \log\{1 + 3.9 \times 10^{-4}\,[Pr] + 10A(1 + 10B)\}$, (4) where $A = pH - 10.64 + 0.011T + 0.737I0.323$ and $B = 1.92 - 0.01T - 0.737I0.323 + \log[Na^+] + (0.651 - 0.494I)(1 + 0.0065[Pr])$ (Eq. 4)

Another approach is to directly measure [HCO_3^-] for fast and high volume blood testing typically utilizing Ion-Selective Electrodes (ISE) in electro-chemical sensor based analytical measurements which typically only measure free and mobile HCO_3^- and thus susceptible to errors due to HCO_3^- interaction with other ions e.g. salicylate ions, etc.

Yet another pragmatic approach is to use our corrected-BE incorporating variation of K_1' as K_1' versus BE (equation 5), corrected for ionic strength, etc. by combining Van Slyke equation according to Siggaard-Anderson or Zander or simplified-Zander and equation 5.

Bicarbonate ion formation equilibrium

While both Sco_2 and pK' in equation 1 are not constants and vary with ionic strength, temperature, pH and protein concentration, etc. the variation of pK' is considerable with temperature and ionic strength (10). With $K_1' = Sco_2 * 10^{-pK'}$, Sco_2 is taken to be reasonably constant at 0.03 mmol/L.mmHg at 37°C. Once the temperature is fixed at 37°C, pK' still varies strongly with ionic strength (10, 11). Hyponatraemia is fairly common and may vary over a range of 80 to 210 mmol/l in plasma Na^+ levels. Abnormal plasma Na^+ levels fluctuations over hours and days in a given patient are not uncommon (10). Hyponatraemia or hypernatraemia i.e. variation in plasma Na^+ levels contributes significantly to variations in K_1'. We find the variation in pK' with ionic strength is particularly evident if logarithmic scale is not used as in K_1' as expressed in equation 5. Such large corrections are very obvious when applied to BE model, since calculation of bicarbonate from equation 2 in Base Excess approach (1, 2) also includes taking the antilog and thus one is confronted by the high level of variations due to pK'. We converted the data in the literature (11) from pK' versus ionic strength to K_1' versus BE when only bicarbonate and strong ions are present and find it to be:

$$K_1' = 2.7346 \cdot 10^{-11} - 0.3692 \cdot 10^{-11} \cdot BE \quad \text{(Eq. 5)}$$

It is further noteworthy, as per the electrical neutrality equation 6, that all the ions are inter-related to reach equilibrium:

$([Na^+] + [K^+] + \ldots - [Cl^-] - [\text{ketones}] - [\text{lactates}]\ldots) + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{-2}] - [OH^-] = 0$ (Eq. 6)

where [A^-] represents the albumin ions.

We start with Van Slyke equation according to Siggaard-Anderson (12) and incorporate our correction for K_1' (or pK') variations.

ctH^+-Siggaard-Andersen(=BE-Siggaard-Anderson) = – (1 – (1 – rc) · φEB) · (($cHCO_3^-$ – $cHCO_3°$) + bufferval · (pH – pH°)) (Eq. 7)

rc = $cHCO_3^-E/cHCO_3^-P$ = 0.57

φEB = ctHbB/ctHbE

ctHbE = 21 mM

$cHCO_3°$ = 24.5 mM

pH° = 7.40

bufferval = βmHb · ctHb + βP

βmHb = 2.3

If the albumin concentration (cAlb) is known, the buffer value of non-bicarbonate buffers in plasma may be expressed as a function of cAlb :

βP = βP° + βmAlb · (cAlb – cAlb°)

βP° = 7.7 mM

βmAlb = 8.0

cAlb° = 0.66 mM

ctH^+Ecf is calculated using ctHbEcf = ctHbB · FBEcf. FBEcf, volume fraction of blood in extended extracellular fluid, is 0.33 by default.

The first term (1 – ctHb/ctHbB) is an empirical factor which takes the distribution of HCO_3^- between plasma and erythrocytes into account. The second term ($cHCO_3^-$ – $cHCO_3°$) titrates the bicarbonate buffer to pH = 7.40 at pCO_2 = 5.3 kPa. The last term titrates the non-bicarbonate buffers (primarily Hb and albumin) to pH = 7.40.

We combine equations 5 and 7 to obtain equation 8 to obtain the corrected Siggaard-Anderson's Van Slyke equation for corrected BE :

corrected-ctH^+–Siggaard-Andersen(= corrected-BE-Siggaard-Anderson) = –(1–(1 – rc) · φEB) · (((2.7346/2.46) $cHCO_3^-$ – $cHCO_3°$) + bufferval · (pH – pH°))/(1 + (1 – (1 – rc) · φEB) . 0.3692 . pCO_2. $10^{(pH-08)}$) (Eq. 8)

For all clinical purposes, the Van Slyke equation according to Zander (13) is the good choice and can be recommended in the following form :

BE-Zander = (1–0.0143 . cHb) . [{0.0304 . P_{CO2} . $10^{(pH-6.1)}$ – 24.26} + (9.5 + 1.63 . cHb) . (pH – 7.4)] – 0.2 . cHb . (1 – sO_2) (Eq. 9)

where the last term is a correction for oxygen saturation (sO_2). Hence, base excess can be obtained with high accuracy (<1 mmol/l) from the measured quantities of pH, pCO_2, cHb, and sO_2 in used.

We combine equation 5 and 9 to obtain equation 10 for corrected BE for Zander's Van Slyke equation :

corrected-BE-Zander = (1–0.0143 . cHb) . [{2.7346 . P_{CO2} . $10^{(pH-8)}$ – 24.26} + (9.5 + 1.63 . cHb) . (pH – 7.4)] – 0.2 . cHb . (1–sO_2)/(1 + (1–0.0143.cHb) . 0.3692 . pco2. $10^{(pH-08)}$) (Eq. 10)

For purpose of illustration of our pragmatic approach, we utilized a simplified Siggaard-Anderson's Van Slyke equation :

$$BE\text{-simplified-Zander} = 0.9287\ (HCO_3 - 24.4 + 14.83\ (pH - 7.4)) \quad \text{(Eq. 11)}$$

We show the results in Table I to also highlight the large variation of BE with pK' according to equation 11 for Pco_2 = 40 mmHg and pH = 7.4.

We combine equations 5 and 11 to obtain equation 12 for corrected BE

$$corrected\text{-BE-simplified-Zander} = 0.9287\ ((2.7346 \cdot 10^{-08} \cdot pCO_2/10^{-pH}) - 24.4 + 14.83\ (pH - 7.4))/(1 + 0.9287 \cdot 0.3692 \cdot pCO_2 \cdot 10^{(pH-8)}) \quad \text{(Eq. 12)}$$

RESULTS AND DISCUSSION

Figure 1 shows the fixed-BE for pK' = 6.1 (assumed constant), exact-BE-simplified-Zander for the measured data points (11) and corrected-BE-simplified-Zander corrected for pK' variability by absorbing pK' (or K_1') versus exact-BE into the BE-simplified-Zander calculations. Note the improvement of corrected-BE-simplified-Zander over fixed-BE for constant pK' = 6.1. The x-axis reflects various data points shown as pK' values.

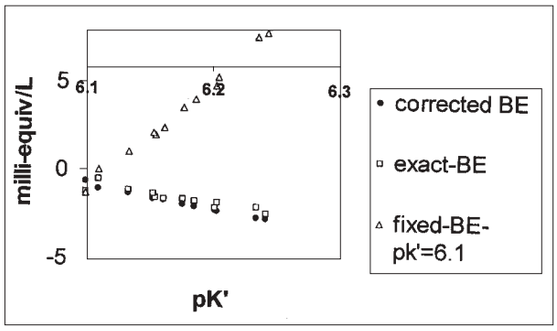

Fig. 1 : Fixed-BE for pK' = 6.1 (assumed constant), exact-BE-simplified-Zander for the measured data points (11) and corrected-BE-simplified-Zander corrected for pK' variability by absorbing pK' (or K_1') versus exact-BE into the BE-simplified-Zander calculations. Note the improvement of corrected-BE-simplified-Zander without having resort to costly and error prone measurements of the ionic strength, etc. thereby reducing health care costs. The X-axis reflects various data points shown as pK' values.

To measure ionic strength requires, depending upon the precision to which one aspires, the measurement of ion concentrations including Na^+, Cl^-, K^+, Ca^{++}, Mg^{++}, sulfate, urate, and lactate with their attendant costs. The problem of cumulative random assay error with so many measured parameters is not trivial and may compromise the very precision needed to directly correct pK' or K_1'. Our pragmatic approach makes such a correction in a cost effective manner by absorbing the variation of K_1' as a function of BE itself without having resort to costly and error prone measurements of the ionic strength, etc. thereby reducing health care costs.

We believe that future K_1' versus BE values will be available experimentally spanning the wide physiological range for healthy individuals and also under critical care conditions. Direct accurate [HCO_3^-] measurements free of all interfering ions in the future is also a good solution to improve the accuracy of the BE approach.

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