Comment on osmotically inactive ions

Matthew B. Wolf

Department of Pharmacology, Physiology, and Neuroscience, University of South Carolina, Columbia, South Carolina

Submitted 8 September 2016; accepted in final form 22 September 2016

TO THE EDITOR: Nguyen et al. (6) attempted to show the physiological significance of the coefficients of their linear regression fit to the data (6) of Edelman et al. (Table 1) and a similar one of Boling et al. (Table 2) in regard to understanding the physiological factors responsible for dysnatremias. An understanding of this clinical condition is very important, but this paper has a number of technical flaws that render its conclusions invalid.

1) The statistical treatment of the data (Tables 1 and 2) in the Nguyen et al. (6) paper is flawed as first suggested by Ring (8) and confirmed here. Figure 1 shows their Table 1 data (open circles) and my linear regression analysis (solid line) obtained using the Sigma Stat computer program. Both the slope (0.88) and Y-intercept (10.0) are quite different from those found by Edelman et al. and also different than their analysis (6) of Edelman’s data: 0.93 and 1.37, respectively. Similarly, their analysis (6) of the Boling data in Table 2 gave somewhat different results (0.487, 71.54) from my analysis of that data (0.461, 73.8) using Sigma Stat.

2) They suggested (6) that a valid estimate of the osmotically inactive Na⁺ and K⁺ could be obtained by extrapolating the regression line to the origin. Figure 1 shows this extrapolation and that the region of 95% confidence (bounded by the dotted lines) grows as the extrapolation gets further from the experimental data region. At the y-axis, it lies between −11 and 32 with 95% confidence and includes zero (no osmotically active electrolytes). Furthermore, the intercept of 10 meq/LW is not statistically significant (P = 0.37). An analysis of the Boling data gives similar results.

3) The assumption of a linear model was questioned by Ring (8) and confirmed herein (see item 4, below). My validated mathematical model of body fluid and electrolytes (9) shows in Fig. 1 that subtracting (i.e., urine loss) of either a mass of NaCl (long-dash) or NaHCO₃ (short-dash) from the normal Na concentration ([Na⁺]pw) produces far different nonlinear decreases in plasma water Na⁺ concentration ([Na⁺]pw), which at best, suggest quite different values if extrapolated.

4) Their present Eq. 2 (Eq. 1, below) to determine [Na⁺]pw was first derived in 2003 as Eq. 2 (2), under the assumption of osmotic equilibrium (equal osmoralties) in the fluid compartments in the whole body. In this derivation, G/Ø was implicitly equal to one. It was changed to its present form in 2004 (4). It was again changed in 2006 (5) by eliminating the G/Ø term and having a factor g/Ø multiply only the first two sets of terms in Eq. 1 (their Eq. 12, Eq. 2, below). This latter equation is flawed as first suggested by Ring (7), subsequently by Dorrington (1), and now from my analysis (see below).

\[
[Na]_{pw} = \frac{G}{\theta} \left[ \frac{Na_{e} + K_{e}}{TBW} \right] + \left( \frac{Osm_{ec} + Osm_{ic}}{TBW} \right) - \left( \frac{Osm_{pw}}{V_{pw}} \right) - \left( \frac{[K]_{pw}}{V_{pw}} \right) \hspace{1cm} (1)
\]

\[
[Na]_{pw} = \frac{g}{\theta} \left[ \frac{Na_{e} + K_{e}}{TBW} \right] + \left( \frac{Osm_{ec} + Osm_{ic}}{TBW} \right) - \left( \frac{1}{\theta} \left( \frac{[K]_{pw}}{V_{pw}} \right) \right) \hspace{1cm} (2)
\]

where the symbols are total exchangeable ion (e), total body water (TBW), extracellular osmolarities (Osm_{ec}), which is the sum of non-Na and non-K plasma water osmoles (Osm_{pw}) and interstitial (i) osmolarities, compartment volume (V), a compartment volume-dependent constant (g) accounting for the Gibbs-Donnan phenomena, an osmolality and compartment volume-dependent factor (g), and a constant converting osmoles to moles and plasma concentration from L plasma to L water (θ).

By the author’s definition for osmol in compartment j, 
\[
(osmol_{j}) = (\theta_{j} - [Na]_{j} - [K]_{j})V_{j}
\]

where θ is osmolality.

Analysis of Equations

Equations 1 and 2 above, may have problems in that [Na]_{pw}, a dependent variable, appears not only on the left-hand side (LHS) of each equation, but also on their right-hand sides (RHS; i.e., in the calculations of [Na]_{pw}, Osm_{ec} and Osm_{pw}). Traditionally, a nonimplicit equation, such as Eq. 1 or Eq. 2, would have the dependent variable, [Na]_{pw}, on the LHS and only constants and independent variables, such as total body masses and volumes on the RHS.

Also, since Na_{e} = \sum_{i=\text{pw,ic}} [Na]V_{i}, then the first two terms inside the brackets ([ ]) in Eqs. 1 and 2 become,
\[
\left( \frac{\theta_{pw}V_{pw} + \theta_{ic}V_{ic} + \theta_{Na}V_{Na}}{TBW} \right),
\]

which equals θ*if all values of θ_{j} = θ* as is the assumption in the 2003 paper (2).

The last two terms in parentheses become,
\[- \theta^{*} + [Na]_{pw}.\]

Therefore, Eq. 1 becomes, [Na]_{pw} = G/\theta[Na]_{pw}, which can be true only if G/θ = 1. Then, Eq. 1 is an identity, yielding no information on the factors responsible for changing [Na⁺]pw. The conclusion is that Eq. 1 has no physiological validity.

Ring (7) first questioned Eq. 2, above, which appeared in an earlier paper (5), because the same result was obtained even
though the volumes and osmolality values were changed to any other values than those in Table 1 of that paper. Later, Dorrington (1) found that algebraic substitution of the terms given (5) on the RHS of Eq. 2, including the definition of g, resulted in the identity, \([\text{Na}\]_{\text{pw}} = [\text{Na}\]_{\text{pw}}\), leading to the conclusion that Eq. 2 has no physiological validity, just as Eq. 1. I also have verified his conclusion.

My overall conclusion is that Nguyen et al. in this paper (6) and Nguyen and Kurtz in their previous ones (2–5) simply rearranged a mass (osmotic) balance equation so that it had the linear form of a regression of Edelman and Boling data and erroneously gave an apparent physiological interpretation to the slope and y-intercept of the regression.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

M.B.W. provided conception and design of research; M.B.W. analyzed data; M.B.W. interpreted results of experiments; M.B.W. prepared figures; M.B.W. drafted manuscript; M.B.W. edited and revised manuscript; M.B.W. approved final version of manuscript.

REFERENCES