Reply

Sir,

In their letter, Ring et al. criticize our new quantitative approach for correcting hypervolaemic hypernatraemia by achieving negative Na\(^+\) and K\(^+\) balance in excess of negative H\(_2\)O balance [1]. Ring et al. stated that our new formula is not simple to use because it requires an estimate of the initial total body water (TBW\(_i\)) and frequent measurements of urinary [Na\(^+\)] and K\(^+\). First, the utility of an equation should not be based on its simplicity of usage, but rather on the extent to which it accurately models human physiology. In this regard, our new formula is derived based on the known empirical relationship between the plasma water sodium concentration ([Na\(^+\)]\(_p\)) and total exchangeable sodium (Na\(_e\)), total exchangeable potassium (K\(_e\)) and total body water (TBW) originally reported by Edelman et al. [2]. Since TBW is a determinant of the plasma sodium concentration ([Na\(^+\)]\(_p\)), any formula used in predicting alterations in the [Na\(^+\)]\(_p\) requires an estimate of TBW\(_i\). For instance, the sodium deficit, free water deficit and Adrogue–Madias formulas all require an estimate of TBW\(_i\). Second, since Na\(_e\) and K\(_e\) are the major determinants of the [Na\(^+\)]\(_p\), alterations in the mass balance of Na\(^+\) and K\(^+\) will result in changes in the [Na\(^+\)]\(_p\). Therefore, measurements of urinary [Na\(^+\) + K\(^+\)] are required to account for changes in the mass balance of Na\(^+\) and K\(^+\) that will result in changes in the [Na\(^+\)]\(_p\). Furthermore, our mathematical model can be legitimately criticized only if it were to assume that the body is a closed system. Therefore, consideration of urinary losses of Na\(^+\) and K\(^+\) by our formula should rather be regarded as a strength, since our formula accounts for the physiologic fact that the body is an open system. It is not clear to us why Ring et al. would prefer a formula that assumes that the body is a closed system.

Ring et al. also claimed to have derived a ‘new ancillary formula…with the intent of avoiding accidents secondary to using the formula given by Nguyen and Kurtz’ [3]. Since the body is an open system, our Equation (4) accounts for infusedate (IVF) and non-infusate (\(E_{\text{input}}\) and \(V_{\text{input}}\)) inputs and renal (urine) and non-renal (\(E_{\text{output}}\) and \(V_{\text{output}}\)) outputs [1]:

\[
([\text{Na}^+]_{p2} + 23.8) \times (\text{TBW}_1 + V_{\text{MB}}) - ([\text{Na}^+]_{p1} + 23.8) \\
\times \text{TBW}_1 - 1.03 \times ([E]_{\text{input}} \times V_{\text{input}} - [E]_{\text{output}} \\
\times V_{\text{output}} - [E]_{\text{urine}} \times (V_{\text{input}} - V_{\text{output}} - V_{\text{MB}})) \\
= -1.03([E]_{\text{urine}} \times V_{\text{IVF}}),
\]

where \(y = 23.8\) in the setting of euclumencism.

In our clinical example, there is no significant non-infusate input and non-renal output. In such clinical settings, Equation (4) can be simplified and rearranged to the following equation:

\[
[\text{Na}^+]_{p2} = (([\text{Na}^+]_{p1} + 23.8) \times \text{TBW}_1 - V_{\text{IVF}} \times 1.03 \\
\times [E]_{\text{urine}} + 1.03([E]_{\text{urine}} \times V_{\text{MB}}))/(\text{TBW}_1 + V_{\text{MB}}) \\
- 23.8.
\]

Therefore, the above so-called new ancillary formula that Ring et al. claimed to have derived to avoid any potential errors in the utility of our formula is simply our Equation (4) in clinical settings where there is no significant non-infusate input and non-renal output.

Ring et al. also argue that our patient’s history is ‘extraordinary’ in that the ‘patient is not stated to be demented, to have diabetes insipidus or osmotic diuresis, or to have been denied access to water...yet this elderly lady with congestive heart failure develops hypernatraemia said to be secondary to furosemide treatment’. In the clinical example, our elderly patient remained hypervolaemic with physical and laboratory findings consistent with congestive heart failure at the time she developed hypernatraemia. Our analysis revealed that the development of hypernatraemia was due to the furosemide treatment. In contrast to what is stated by Ring et al., furosemide treatment can predispose to the development of hypernatraemia due to the hypotonic urinary losses [3]. It is ironic that Ring et al. argue that osmotic diuresis can result in hypernatraemia and yet furosemide therapy cannot cause hypernatraemia. It is well known that both osmotic diuresis and furosemide lead to urinary excretion of H\(_2\)O in excess of Na\(^+\) and K\(^+\), thereby predisposing to the development of hypernatraemia [3]. Second, we disagree with Ring et al. that our patient does not have a component of diabetes insipidus. It is well appreciated that furosemide can cause a decrease in urinary concentrating ability due to interference with the countercurrent mechanism by inhibiting sodium chloride reabsorption in the thick ascending limb of the loop of Henle [4]. This is the reason why diuretic-induced hyponatremia is caused almost exclusively by thiazide diuretics [4]. Although furosemide can predispose to the generation of hypernatraemia, hypernatraemia cannot occur unless there is a defect in the thirst mechanism or inadequate access to H\(_2\)O [3]. Therefore, our elderly patient likely has a defect in her thirst mechanism. However, it is important to appreciate that a patient with a defect in the thirst mechanism can develop hypernatraemia even if the patient is not demented or has adequate access to H\(_2\)O.

Our new quantitative approach is derived based on the known empirical relationship between the plasma sodium concentration ([Na\(^+\)]\(_p\)) and total exchangeable sodium (Na\(_e\)), total exchangeable potassium (K\(_e\)) and total body water (TBW): [Na\(^+\)]\(_p\) = 1.03(Ke + Na\(_e\))/TBW - 23.8 [2, 5]. Ring et al. argue that the ‘modelled intercept term 23.8 from Edelman is very uncertain with 99% CI including 0’. In a previous letter, Ring also argues that the slope of the Edelman equation should be 1 [6]. However, Ring’s assertion not only is not supported by physiologic and clinical data but also is incorrect based on theoretical principles that govern certain factors that modulate the distribution of Na\(^+\) [7–9]. We have previously demonstrated that there are theoretical and physiologic considerations independent of the empirical data in Edelman’s study, which support Edelman et al. that the slope is greater than unity and the \(y\)-intercept must have a non-zero value [7–9]. If the slope and \(y\)-intercept of the Edelman equation were to be 1 and 0, respectively (as assumed by Ring et al.), then only alterations in the mass balance of Na\(^+\), K\(^+\) and H\(_2\)O will result in a change in the [Na\(^+\)]\(_p\). We therefore...
welcome Ring et al. to provide a scientifically valid explanation as to how one can account quantitatively for all the causes of the dysnatremias resulting from factors that do not alter the value of the \( (N_{ae} + K_{e})/TBW \) term in the Edelman equation such as (1) changes in the \([Na^+]_{b} \) due to inter-compartmental water shifts due to non-\( Na^+ \) and non-\( K^+ \) osmolites such as hyperglycaemia, mannitol, sucrose, maltose and contrast agents; (2) transcellular shifts of \( Na^+ \) and \( K^+ \) in hypokalaemia-induced hyponaetremia and (3) a component of the \( N_{ae} \) and \( K_{e} \) is osmotically inactive and incapable of modulating the \([Na^+]_{b} \). Moreover, based on the measured \( N_{ae}, K_{e}, TBW \) and \([Na^+]_{pw} \) in Edelman’s study [2], the ratio of \( (N_{ae} + K_{e})/TBW \) is significantly greater than the \([Na^+]_{pw} \). Given that the ratio of \( (N_{ae} + K_{e})/TBW \) is significantly greater than the \([Na^+]_{pw} \), we welcome Ring et al. to provide a mathematical explanation as to how one can equate the ratio of \( (N_{ae} + K_{e})/TBW \) to the \([Na^+]_{pw} \) if the slope and \( y \)-intercept of the Edelman equation were to be 1 and 0, respectively (as argued by Ring et al.).

Ring et al. also argue that our new formula ‘would not be much helped’ since it requires frequent monitoring of urinary \( Na^+, K^+ \) and \( H_2O \) losses to guide further adjustments in the fluid prescription. We disagree with this simplistic view. We feel that taking a quantitative approach to adjusting the rate of fluid administration based on ongoing urinary losses is a more logical approach than simply guessing blindly at the rate of fluid administration. Moreover, consideration of ongoing urinary hypotonic loss is particularly relevant in the treatment of hypernatremia, since ongoing urinary loss of \( H_2O \) in excess of \( Na^+ \) and \( K^+ \) induced by furosemide would tend to result in a worsening of the hypernatremia if not accounted for.

Lastly, Ring et al. also questioned why our patient did not exhibit the expected increased \( Na^+ \) excretion. Although the urinary \([Na^+] \) was not exceedingly high \([Na^+]_{urine} = 63 \text{ mmol/L} \), our patient did exhibit a significant natriuresis \((479 \text{ mmol of } Na^+ \text{ excreted}) \) since the total urinary output was \(~7.6 \text{ L} \). Indeed, reliance on urinary \([Na^+] \) as an estimate of urinary \( Na^+ \) excretion can be misleading since urinary \([Na^+] \) is not only a function of the quantity of \( Na^+ \) excreted but also a function of the urinary volume excreted.

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**Oral calcium load and fractional intestinal calcium absorption**

Sir,

Heinrich et al. [1] examined the effect of calcium carbonate intake, as compared to that of sevelamer intake, on intestinal calcium absorption and urinary calcium excretion in healthy human volunteers. The authors reason that under steady-state conditions urinary calcium excretion ‘corresponds’ to calcium load in healthy subjects. This statement is correct for adult individuals but only for net calcium absorption from the gut, that is taking into account total intestinal calcium absorption minus calcium entering the gut lumen via intestinal, biliary and pancreatic secretions. The authors claim that by determining urinary excretion of calcium they are able to measure ‘fractional intestinal absorption’ of calcium. We think this claim is incorrect. To determine fractional intestinal absorption one has to use an isotope method, administering either a single calcium isotope [2] or two different calcium isotopes [3] together with ‘cold’ calcium and then calculating fractional absorption based on radioactivity decay in the blood. The best way to determine net absorption is to carry out balance studies. Admittedly, these methods are time and energy consuming.

When Heinrich et al. acutely switch their healthy volunteers from a dietary calcium intake of 36 mmol/day to 76 mmol/day, by adding 40 mmol/day elemental calcium in the form of calcium carbonate, the individuals are no longer in the steady state for at least some days. Following changes in calcium intake, long-term balance studies have shown that a delay of at least 30 days is necessary to reach the steady state [4]. Under non-steady-state conditions, urinary calcium excretion does no more reflect oral calcium intake.

Considering the above shortcomings, it is not surprising that the estimates of fractional calcium absorption values in their healthy volunteers, in the presence or absence of an additional oral calcium load, namely 8.7–14.8%, are much lower than the values that are generally reported in the literature using validated methods, namely 20–40% [5,6].