



EDITORIAL COMMENT

Formulas for fixing serum sodium: curb your enthusiasm

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Abstract

A variety of formulas have been proposed to predict changes in serum sodium concentration. All are based on an experiment done over 50 years ago by Edelman, who derived a formula relating the plasma sodium concentration to isotopically measured body sodium, potassium, and water. Some of these formulas fail because they do not include urinary losses of electrolytes and water. Even those that include these essential variables are not accurate enough for clinical use because it is impractical to adjust calculations to rapid changes in urinary composition, and because the formulas do not account for changes in serum sodium caused by internal exchanges between soluble and bound sodium stores or shifts of water into or out of cells resulting from changes in intracellular organic osmolytes. Nephrologists should curb their enthusiasm for predictive formulas and rely instead on frequent measurements of the serum sodium when correcting hyponatremia and hypernatremia.

Key words: hyponatremia, hypernatremia, hypertonic saline, organic osmolytes

Nephrologists love formulas. It is fun to mathematically predict what nature is about to do or to explain what it has already done. Formulas elevate us above our colleagues and our students, who gaze in awe as we take to the blackboard to explain acid–base and fluid electrolyte problems that often leave them baffled.

However, it is important that we do not get too carried away with our mathematical friends. Most formulas we use are estimates based on clinical reasoning, limited clinical data or biochemical measurements of uncertain validity. The fractional excretion of sodium (FENa) gives us an estimate of fractional sodium excretion, but it is based on the serum and urine creatinine concentrations, which provide an imperfect estimate of glomerular filtration; its predictive value for distinguishing prerenal azotemia from other causes of kidney injury is based on very limited data. A correction factor that we used for years to correct the serum sodium for the osmotic water shift caused by hyperglycemia was based on armchair reasoning [1]; another estimate, which many of us adopted in its place, was based on a single small experiment that raised blood glucose in volunteers with

somatostatin infused with 5% dextrose in water [2]. The transtubular potassium gradient (TTKG), which we have used to define potassium secretion in the aldosterone-sensitive distal nephron, is based on clinical reasoning augmented by laboratory experiments that proved to be flawed; its creators recommend that it not be used, but many nephrologists still cling to it [3, 4].

In this issue of *Clinical Kidney Journal*, Hahna *et al.* [5] assess the accuracy of four equations that have been proposed to predict the response of the serum sodium concentration to intravenous fluids containing various concentrations of sodium and potassium; none of the forecasts were precise enough to guide therapy. All of these formulas are based on an experiment done >50 years ago by Edelman *et al.* [6], who identified a group of patients with widely varying serum sodium concentrations; measured exchangeable sodium, exchangeable potassium and total body water using isotopes; and then, using linear regression, derived a formula relating the sodium concentration in plasma water to these variables. The equation that emerged had a y-intercept, i.e. the regression line did not pass through zero as would be

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expected if sodium and potassium were simply solutes dissolved in a volume of water [7]. In fact, a substantial fraction of the sodium measured isotopically is not free in solution, but is actually bound to large macromolecules called proteoglycans, in skin, cartilage and bone [8].

There are several reasons why formulas may fail to accurately predict the response of serum sodium concentration to our therapies. The serum sodium concentration is determined by the amount of sodium and potassium dissolved in body fluids, and by the volume of body water:

$$\text{Serum [Na]} = \frac{\text{Total body soluble (Na + K)}}{\text{Total body water}}$$

Many clinicians and some formulas focus solely on the effect of intravenous fluids on this relationship: a solution whose concentration of (Na + K) is higher than that of plasma is expected to raise the serum sodium concentration, while a solution with a lower (Na + K) concentration is expected to lower it; the magnitude of the response is calculated with an algebraic reformulation of the Edelman *et al.* relationship that adds the intravenous solution's electrolyte content to the numerator and its volume to the denominator of the equation [9].

Predictive formulas that ignore urinary electrolyte and water losses are doomed to failure. It should be obvious that net balances of sodium, potassium and water (input – output) must be considered [10]. Urinary electrolyte and water losses often have a greater impact on the serum sodium concentration than do intravenous fluids [8]. The serum sodium concentration of a hypernatremic patient with complete diabetes insipidus who excretes 12 L of dilute urine daily (500 mL/h) will continue to rise during the infusion of 5% dextrose in water at 250 mL/h; formulas based only on fluid intake will erroneously predict correction of hypernatremia by 1 mEq/L/h.

Some formulas take urine losses into account, requiring measurements of urine sodium and potassium concentrations and urine volume. However, such measurements are single frames of what is often a complex movie; when treating hyponatremia, urine composition may change abruptly during the course of therapy. For example, consider a patient with hyponatremia caused by iatrogenic syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to desmopressin. The urine electrolyte concentration may be higher than plasma at presentation, but if desmopressin is discontinued, the urine will become dilute once the antidiuretic effect of the drug has abated; urine electrolyte concentrations will then rapidly fall while urine volume increases, and the serum sodium concentration will increase far more rapidly than the formula predicts.

Conversely, if saline solutions are given to patients with persistent SIADH, volume expansion will eventually provoke a natriuresis, and, if the urine osmolality is higher than plasma osmolality, excretion of salt in a hypertonic urine can actually cause the serum sodium to fall, the opposite of the formula-predicted response [11, 12].

An unanticipated water diuresis is quite common during the course of therapy of severe hyponatremia and often leads to inadvertent overcorrection. In one retrospective series of patients with serum sodium concentrations <120 mEq/L who were treated with 3% saline, the increase in serum sodium exceeded the increase predicted by the original Adrogue–Madias equation (based solely on the initial serum sodium and the composition of intravenous fluids) in 74.2% of patients; the average correction in overcorrectors was 2.4 times the predicted. Inadvertent overcorrection was due to documented water diuresis in 40% of patients [13]. The cause of water retention in most patients with

severe hyponatremia is reversible. As soon as the cause of water retention (hypovolemia, thiazide diuretics, antidepressants, desmopressin, cortisol deficiency or transient SIADH due to pain, stress or nausea) is eliminated, antidiuretic hormone levels become maximally suppressed, and the ensuing water diuresis may increase the serum sodium concentration over 2 mEq/L/h, equivalent to the effect of infusing 3% saline at 150 mL/h. To avoid overcorrection, the clinician must either match urine water losses with 5% dextrose in water, or stop the losses by administering desmopressin [14, 15]. Alternatively, such a water diuresis can be anticipated, and treated proactively with desmopressin at the outset of therapy, creating a state of iatrogenic SIADH, in which urinary water losses are eliminated as a variable; the serum sodium concentration is then increased with the concurrent infusion of 3% saline [15–17]. With the concurrent administration of desmopressin and 3% saline, the increase in serum sodium concentration is more predictable, but the actual increase in serum sodium concentration may still deviate from what formulas project.

The Nguyen–Katz equation is the most rigorous predictive formula, because unlike others, it includes the pesky y-intercept found in Edelman *et al.* original linear regression [18]. As mentioned earlier, the intercept likely has biological meaning; it reflects the insoluble sodium bound to anionic sites on proteoglycans in skin, cartilage and bone. Inaccurate predictions will still occur with this equation if urinary composition changes during the course of therapy. However, even if the electrolyte concentrations and volume of all intake and output could be measured continuously, and changes in composition captured and counted, it is still possible that the actual sodium might deviate from the concentration predicted by the equation. The Nguyen–Katz equation assumes that the intercept in Edelman *et al.* equation is constant. In fact, there is evidence that sodium bound to proteoglycans can serve as a reservoir that can either absorb excess sodium from the soluble pool or contribute to it when sodium is in short supply; such exchanges between soluble and bound sodium pools would make the intercept a variable rather than a constant.

Most predictive equations assume that electrolytes are the only solutes that alter the serum sodium concentration. This is not always true. Clinicians are familiar with the effect of hyperglycemia and exogenous solutes like mannitol on the serum sodium concentration. Intracellular organic osmolytes may also affect the serum sodium concentration. These solutes play an important role in the adaptation of the brain to hyponatremia and hypernatremia; depletion of brain cell osmolytes in hyponatremia and accumulation of extra osmolytes in hypernatremia minimize the change in cell volume that occurs in these disturbances [8]. Organic osmolytes are also present in other cells and could potentially alter the relationship between body electrolytes and serum sodium concentration [19]. For example, depletion of intracellular organic osmolytes in response to chronic hyponatremia would result in a shift of intracellular water to the extracellular fluid, minimizing cell swelling, but lowering the serum sodium concentration. Repletion of cell osmolytes during correction of hyponatremia would result in a shift of water back to the cells, and a greater increase in serum sodium concentration than would be predicted by any formula based on the Edelman *et al.* equation. Such a phenomenon was suspected in a series of severely hyponatremic patients treated with 3% saline and desmopressin [17]. One would expect that with time, because of volume expansion, urinary losses of sodium would accelerate during administration of hypertonic saline, blunting the effect of the intravenous fluid on the serum sodium concentration. In fact, the opposite occurred; the increase in serum

sodium in response to hypertonic saline was greater on the second day of the protocol, as might occur with time-dependent repletion of lost intracellular organic osmolytes.

Minor differences between actual and predicted changes in the serum sodium concentration are more important now than they had been in the past. It was once fashionable to 'half-correct' the serum sodium concentration within a few hours. It is now known that in patients with severe hyponatremia, this practice often leads to osmotic demyelination syndrome [20, 21]. Most authorities now recommend correction rates of 4–6 mEq/L/day to avoid this complication [22, 23]. With goals this small, a 1–2 mEq/L deviation from predicted increases can no longer be tolerated. Nephrologists should curb their enthusiasm for predictive formulas and rely instead on a strategy that may be less intellectually satisfying, but ultimately more successful: when fixing the serum sodium concentration, measure the serum sodium concentration and measure it often.

(See related article by Hanna *et al.* The utility and accuracy of four equations in predicting sodium levels in dysnatremic patients. *Clin Kidney J* (2016) 9: 530–539.)

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