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
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 hyponatremic 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 hyponatremia 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, 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 hyponatremia; depletion of brain cell osmolytes in hyponatremia and accumulation of extra osmolytes in hyponatremia 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 overcorrection, 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.)

References