The Adrogue-Madias Formula Revisited

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Few subjects engender as much heated discussion at various nephrology meetings as the strongly held views by advocates of various approaches to the management of hyponatremia (1). The controversy as to how these patients should best be treated can be traced to the fact that even in a specialty such as ours, which already suffers from a dearth of properly conducted prospective, randomized, controlled trials, not a single such trial is designed to address the optimal management of this most common of electrolyte disorders. There are, therefore, no clearly established and uniformly agreed-on national or international guidelines (2), and those that are put forth in various publications (2–7) are based primarily on retrospective observational analyses on a limited number of patients (7–12). None has the virtue of comparing prospectively two or more therapeutic options and monitoring for well-defined neurological outcomes in a randomized, controlled trial or even in a robust prospective, observational trial (13). Ultimately, the published recommendations are largely opinion based and reflect the experience of the various authors.

In the midst of the controversy that surrounds the rate and magnitude that should guide the treatment of hyponatremia, the most accepted intervention is the one that calls for the use of hypertonic sodium chloride (3% NaCl) to treat patients who have severe hyponatremia (Na <125 mEq) and present with marked neurologic symptoms, especially seizures. This intervention is designed to reverse promptly the accompanying cerebral edema that could in turn result in tentorial herniation and culminate in the patient's death. There is, however, essentially no literature as to the use of this approach. In this regard, the accompanying article by Mohmand *et al.* (14), despite being a retrospective review, makes a significant contribution to the literature, because the authors relate their extensive experience with 62 patients who were treated with hypertonic saline. We learn from their experience that the infusion need not be given solely in an intensive care setting; more than half of the patients were treated on the medical floors. Likewise, we learn that the indication for hypertonic saline need not be limited to patients with seizures, and hypertonic saline can be used in those in whom isotonic saline or water restriction is unlikely to raise the serum sodium concentration. Such patients can be recognized

by a high (>1) ratio of urinary to serum sodium and potassium concentrations (15). The report also reveals that when administered by experienced nephrologists who carefully monitor the patients, the increment in serum sodium can be achieved promptly and kept within acceptable safe limits. Thus, none of the patients developed the dreaded osmotic demyelination syndrome or any significant new neurologic deficits. It must be noted, however, that the rates of infusion used were very conservative, significantly below the 1 ml/kg per h that is usually suggested, resulting in a rate of correction of only approximately 0.5 mEq/L per h. The institution at which this experience was gathered is acutely aware of the dangers associated with overcorrection, and their cautious approach to the use of the hypertonic solutions should be a guide to other physicians contemplating the use of this solution.

Perhaps the most significant aspect of the report by Mohmand *et al.* (14) relates to the attempt to determine whether the formula put forth by Adrogue and Madias (5) accurately predicts the change in serum sodium that can be expected from a given infusion rate. Although various formulas have been proposed to aid in predicting the increment in serum sodium that would accompany the infusion of either normal saline or hypertonic saline (2), the aforementioned Adrogue-Madias formula is the one most widely used. A recent article (16) scrutinized the use of the formula in both hypo- and hypernatremic patients. Of the 204 patients with hyponatremia in this study, only 10 received hypertonic saline, a number too low to be independently analyzed. The great majority of the patients received normal saline. The authors reported that in most, the formula predicted closely the observed increase in serum sodium. Nonetheless, in every subgroup, the achieved serum sodium was higher than the anticipated one, but the difference failed to reach statistical significance because of the low number of patients in each subgroup. The discrepancy was particularly marked and actually achieved statistical significance in the hypovolemic group, with the rise in serum sodium being two to three times larger than predicted by the formula. A similar difference with statistical significance was noted in the primary polydipsia group and in the hypernatremic patients (16). In the article Mohmand *et al.* (14) in this issue, the achieved serum sodium exceeded the one predicted from the Adrogue-Madias formula in three of four patients whose serum sodium was <120 mEq/L at the outset, the most likely group to be treated with hypertonic solutions.

A number of factors could explain the discrepancies between

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calculated and observed changes in serum sodium noted in the article and by others who have used the formula. The formula is based on the original empirically derived relationship among exchangeable sodium, exchangeable potassium, and total body water originally reported by Edelman *et al.* (17). The shortcomings of the original formula have been elegantly described by Nguyen *et al.* (18). Furthermore, the formula does not allow for the increase in serum sodium concentration that accompanies the administration of potassium in this frequently potassium-depleted group of patients (19). Whether exchangeable sodium and potassium are themselves constant has been called into question by observations suggesting that sodium can be activated or inactivated under some circumstances (20); however, probably the primary shortcoming of the formula is its failure to assess ongoing renal and extrarenal losses. Although this may not be important in the first 2 to 4 h of treatment, it could be critical over a longer time frame, resulting in undesirably high rates of corrections over 24 and 48 h. This is particularly critical in settings in which the nonosmotic release of vasopressin is no longer operant (*e.g.*, the restoration of volume in hypovolemic patients) and a water diuresis ensues, resulting in the excretion of electrolyte-free water. Barsoum and Levine (21) proposed a formula that incorporates all of these variables, but its complexity makes it impractical for clinical use; therefore, although the Adrogue-Madias formula or any other published formula (2) can provide an initial prediction, there is ultimately no substitute for the close monitoring of the serum sodium, as well as the urinary electrolyte content of patients with severe symptomatic hyponatremia (6). This monitoring makes it more likely that a safe rate of correction will be achieved. Furthermore, when the correction is excessive, this allows for the prompt administration of free water with or without DDAVP to mitigate the increase and even relower the serum sodium. Such an approach should significantly decrease the risk for the neurologic complications that inappropriately make physicians reluctant to treat patients with this common electrolyte disorder.

Disclosures

None.

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