Pediatr Nephrol (2007) 22:163–166
DOI 10.1007/s00467-006-0309-x

EDITORIAL COMMENTARY

Effect of hypoxia on the cerebral adaptation to acute hyponatremia in experimental animals

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Received: 16 May 2006 / Revised: 22 August 2006 / Accepted: 23 August 2006 / Published online: 17 October 2006
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Keywords Hyponatremia · Hypoxia · Cerebral edema · Cell volume regulation

Anyone who has been reading the literature about hyponatremia in steady doses over the past 20 years could become exasperated and conclude that the endless stream of articles addressing the pathogenesis, epidemiology, manifestations, diagnosis, and proper management of this electrolyte disorder are nothing more than intellectual squabbling. It would be easy to lose hope of shedding new light or reaching a consensus on this contentious issue.

However, in actuality, there is much that nephrologists actually agree about on this topic. First, it is widely recognized that hyponatremia is the most common electrolyte disturbance in hospitalized patients [1]. In addition, an abnormally low serum sodium concentration can occur in the context of a low, normal, or expanded extracellular fluid volume [2, 3]. The syndrome of inappropriate anti-diuretic hormone (ADH) release probably accounts for a large percentage of cases, and it reflects abnormal vasopressin release that can be triggered by either osmotic or non-osmotic stimuli [4]. Finally, the primary target organ in patients with hyponatremia is the brain, and they are susceptible to developing acute cerebral edema due to the movement of water down its gradient from the extracellular to the intracellular compartments [2, 3]. It is at this point that the going gets tougher. The debate begins to heat up noticeably when people start to ask what is the timeframe during which hyponatremia is a life-threatening problem? What is acute and what is chronic? The argument intensifies even further when the pathogenesis of the neuropathological lesions in the brain in patients with hyponatremia is addressed. Is it the consequence of the electrolyte disturbance per se, or the treatment used to correct the low serum sodium concentration? Is the damage solely due to osmolal injury or are other factors such as elevated arginine vasopressin (AVP) levels or reduced cerebral perfusion involved in the process? Needless to say, things are almost out of control when prognosis and liability are raised in the context of the management of a patient with hyponatremia.

Allan Arieff and his colleagues have been studying hyponatremia for over three decades and have published numerous reports about the changing profile of the entity and the impact of therapy on patient outcomes. Because of the logistical constraints involved in systematically evaluating different treatment regimens in the acute setting, they have tried to systematically translate lessons learned from experimental animals to the bedside. For example, they have shown that the risk of developing clinical symptoms as a consequence of hyponatremia is not the same in all patients. Juvenile animals and menstruating female animals manifest increased cerebral edema in response to acute hyponatremia compared to male counterparts and postmenopausal females. This is reflected by increased brain sodium content and reduced activity of the Na-K ATPase, which may be inhibited by circulating estrogens [5]. Interestingly, these findings are paralleled by data in patients which suggest that the young children and

Supported by NIH DK70341 to the author.

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menstruating women are disproportionately affected by hyponatremia [6].

Over the years, Arieff has been a steady and vocal proponent of the need for the rapid correction of hyponatremia to prevent sudden neurological deterioration and permanent functional sequelae as a result of untreated cerebral edema. He has maintained that it is sustained hyponatremia that directly causes brain injury and leads to long-term neurological disability. However, there is no unanimity about the cause of neurological injury during the development of acute hyponatremia and its correction in experimental animals. Prominent groups, including Sterns et al. [7] and Soupart and Decaux [8], have published data at marked variance with Arieff's findings. Based on these reports, there have been opposing voices urging slower rates of correction and arguing that the treatment is worse than the disease [9]. These nephrologists assert that the overzealous correction of hyponatremia is responsible for causing the osmotic demyelinating syndrome.

Amazingly, Arieff et al. still have the courage to tread into this medical minefield again with new studies that add to their contention that hyponatremia is a medical emergency that warrants urgent treatment. In a recent series of experimental studies published in the Kidney International journal [10], I can report back from the paper battlefield that their work remains timely and relevant, and has the potential to impact on the clinical approach to patients with acute hyponatremia. They begin their work with the observation that the majority of patients with acute hyponatremia are observed to be hypoxic when they first develop symptoms related to the electrolyte abnormality. For example, in a prospective study of 16 children who developed hyponatremia (serum Na+ concentration 115± 7 mmol/L), 3–120 h after hospitalization for a minor illness, the mean arterial oxygen was 6±1.5 kPa [11]. Similarly, in 65 adult patients (25 men and 40 women), with postoperative hyponatremia, among the 34 who developed permanent brain damage or died (33 were women), their mean arterial pO_2 at diagnosis was significantly lower than in the hyponatremic men, 34±5 versus 91±3 mmHg, $p<0.001$ [6]. Finally, Arieff et al. has linked the hypoxia that occurs in hyponatremic encephalopathy to non-cardiogenic pulmonary edema and hypercapnic respiratory failure [12].

To better define the contribution of hypoxia to the severe neurological dysfunction and injury in acute hyponatremia, they used rabbits and induced hyponatremia over 4 hours to 4 days with a combination of subcutaneous injections of vasopressin and nasogastric installation of free water [10]. The serum sodium concentration fell abruptly into the range 115–120 mmol/L. The brain adaptation to the acute hyponatremia was markedly impaired if the animals were also rendered hypoxic by exposure to a 5% oxygen environment. The presence of concomitant hypoxia resulted in a significantly higher brain water and osmolality. Whereas in rats the increased osmolality was accounted for by higher lactate levels, in rabbits, it reflected elevated brain sodium content. In follow-up experiments with rats, the combination of subacute hyponatremia of 4 days duration with hypoxia reduced cerebral perfusion by more than 50%, and led to more prominent histopathological signs of acute brain injury, including focal areas of neuronal loss, proliferation of small vessels, an increased number of macrophages, and peripheral gliosis.

At the outset, it is important to underline the need to be thoughtful in interpreting animal models of human disease and be vigilant against inappropriate extrapolation when designing therapeutic strategies to treat the condition. Thus, there are several aspects of this study that warrant careful attention. First, it is odd and unclear why different rodent species were utilized in the various protocols. Second, it is striking that, in these experimental models, there is no evidence that hypoxia occurred spontaneously and it had to be superimposed on the hyponatremia by exposure to a low-oxygen atmosphere. Third, the degree of hypoxia was more severe than is usually encountered in clinical practice and could have caused mortality or cerebral lesions as a single factor. Fourth, the use of AVP in oil given as a subcutaneous injection to induce hyponatremia may lead to erratic absorption and widely varying hormone levels. In addition, the exogenously administered AVP could directly interact with V1 receptors and trigger cerebral vasoconstriction. Finally, the authors may be unintentionally compounding the confusion about this contentious topic and inhibiting the widespread acceptance of their findings by labeling the 4-day protocol as acute hyponatremia. Most of the clinical morbidity and mortality associated with untreated hyponatremia has been documented in the postoperative setting where the electrolyte abnormality develops quite suddenly within 12–24 h. It might be advisable to limit future studies to animals with hyponatremia for, at most, 2 days, so that appropriate conclusions about the optimal management can be drawn from this work. This suggests that inferences to clinical practice should be made cautiously at best.

Despite the methodological limitations of this study outlined above, the morbidity and mortality associated with hyponatremia is much higher in patients with concomitant hypoxia. The findings in these experiments go a long way to explaining this observation by demonstrating that hypoxia interferes with the normal brain cell volume regulatory adaptation to lower intracellular osmolality in the face of plasma hypoosmolality. This is plausible because, in addition to the activation of membrane channels that facilitate the efflux of organic osmolytes such as sorbitol, energy is required to actively extrude sodium and

other electrolytes from the cerebral cell. These processes are certain to be aversely impacted by hypoxia. If hypoxia impairs cerebral perfusion, then an open feedback loop will be initiated that will aggravate the capacity of the cell to adaptively lower its osmolyte content and prevent further cell swelling.

What are the implications of these important laboratory findings? I believe that these studies should be analyzed in the context of patients with acute hyponatremia that has developed over less than 2 days. My recommendations for management are summarized in the Table 1. They are offered as general guidelines for all cases of acute hyponatremia in pediatric patients with the understanding that they may need to be modified to account for specific features in an individual patient. They remain only opinions and should be viewed accordingly. Results from experimental and clinical investigations indicate that, because of the frequent association of hypoxia in these circumstances, these patients must be considered at very high risk of neurological complications. Thus, it should be standard practice that all pediatric patients with acute severe hyponatremia be promptly admitted to an intensive care unit and closely monitored for changes in mental status, vital signs, and fluid and electrolyte balance. Because the deteriorations can be sudden and catastrophic, it is advisable to administer hypertonic 3% saline in doses sufficient to quickly raise the serum sodium concentration by 3–5 mmol/L over the first 4 hours. This recommendation differs from the one offered by Kokko for adult patients in his commentary on Arieff's paper [13]. It is based on the paper by Sarnaik et al. [14], which remains the only study that compares the efficacy of hypertonic saline versus anticonvulsants in the treatment of hyponatremic seizures. The benefit of hypertonic saline, given in this manner, has only been demonstrated in patients with neurological symptoms. Thus, an argument could be made to restrict the use of hypertonic saline to children with these complaints and avoid the administration of this solution in those with acute hyponatremia who are alert and fully responsive. I acknowledge that the infusion of hypertonic saline to patients with severe acute hyponatremia who are clinically well has never been studied in a well designed trial. There are not even single-center retrospective data to support this practice. However, my opinion is that the consequences of inadequately treated acute hyponatremia are too great and it is worth taking reasonable steps to avoid the catastrophic consequences of sudden-onset cerebral edema. Moreover, if patients are admitted to an intensive care unit for care, then the risks of moderate volumes of 3% saline designed to raise the serum sodium concentration by 3–5 mmol/L are low enough to justify its use. I suggest that this practice be monitored to ensure the safety of administering 3% saline to all children with severe acute hyponatremia regardless of symptoms. There is no place for fluid restriction as a sole intervention in patients with acute severe hyponatremia. Time really is of the essence and delays in initiating effective therapy or relying on treatments that require extended periods of time to take effect are misguided. This recommendation is even more pressing in patients with incipient signs of cerebral edema. It is not germane to asymptomatic patients who are coincidentally found to have hyponatremia that is likely to be secondary to long-term net sodium losses.

Once the acute situation has been stabilized, the serum sodium concentration should be gradually raised by 20–25 mol/L or to approximately 130 mmol/L, whichever yields a smaller net increment, over the next 48 hours. The composition of the fluid should be based on standard calculations of maintenance and deficit fluids and will generally be approximately 100 mmol/L, between 1/2 (0.45%) and normal (0.9%) saline solution. The Adrogue-Madias formula can be used to estimate the change in serum sodium concentration in response to the infusion of a particular type and volume of sodium chloride solution [15]. While there are those who advocate the routine use normal saline for the full correction of hyponatremia to repair sodium deficits, I am of the opinion that acute severe hyponatremia is more commonly associated with the expansion of the extracellular fluid compartment and that following through with the calculations will yield a fluid

Table 1 Recommendations for fluid and electrolyte management of pediatric patients with acute hyponatremia

Phase	Fluid	Target increase in serum Na+	Timeframe	Concomitant issues
Short-term	3% NaCl	3–5 mmol/L	First 4 hours	1. Admit to ICU for observation 2. Maintain pO_2 in normal range
Extended	Composition based on calculated maintenance and deficit requirements, generally yielding 0.45% NaCl. If there is significant hypovolemia, 0.9% saline is the appropriate fluid	20–25 mmol/L	48 hours	1. Adjust maintenance fluids if there is fever, tachypnea, or disrupted skin integrity 2. Replace ongoing losses with solution containing equivalent Na+ concentration

containing a sodium concentration in the range of 70–100 mmol/L. In the child with acute severe hyponatremia and symptoms of extracellular fluid volume contraction, normal saline is the appropriate solution for the initial fluid resuscitation phase and maintenance therapy until the volume disturbances are resolved. I think that the heated controversy over fast versus slow correction obscures a general agreement about how to manage hyponatremia once the acute neurological consequences are averted. Finally, it is important to remember that the proper treatment of acute hyponatremia does not reflect on standard intravenous fluid therapy. While aggressive treatment is warranted for patients with acute hyponatremia, the routine use of isotonic saline solutions to prevent hyponatremia and the deleterious consequences of cerebral edema still requires careful clinical trials to verify safety and efficacy [16]. I recognize that uniformity of practice is highly unlikely in these circumstances and offer these recommendations as one man's opinion. I welcome further discussion in the interests of improving practice.

Medical progress usually occurs in small steps. Single studies are rarely sturdy enough to support complete alterations in clinical practice and my recommendations should be considered tentative at best, valid until the next best study is performed. This caveat applies even more when trying to apply lessons learned from experimental studies. Nonetheless, if reports such as the one by Arieff et al. [5] are viewed within the context of a life's work and interpreted within the current state of knowledge about a given disease process, they can be helpful in defining how to treat difficult conditions such as acute hyponatremia.

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