Editorial

Recent updates and future perspectives in the treatment of electrolyte disorders

Antonios H Tzamaloukas*[1,2] & Robert H Glew[3]

"Elucidation of the chemistry and function of the molecules that are involved in the feed-forward process could lead to new therapeutic methods."

Fluid and electrolyte abnormalities are common in hospitalized patients. Their management constitutes major therapeutic challenges. Recent studies have documented that abnormalities in serum electrolyte concentration are also encountered in a substantial proportion of outpatient populations, particularly older subjects, and that even modest electrolyte abnormalities carry a mortality risk [1]. This article will review abnormalities of the two monovalent cations, sodium and potassium. We will discuss new developments in the management of these abnormalities and suggest future directions of research that have the potential to improve the outcomes of hyponatremia and hyperkalemia.

Dysnatremias

Dysnatremia is common in outpatients [1] as well as critically ill hospitalized patients [2]. New developments have enhanced our understanding of the manifestations and treatment of hyponatremia. Hyponatremia is the most frequent electrolyte disturbance in an outpatient setting [1]. While the clinical manifestations of severe hyponatremia have been widely recognized, only recently has it been established that even mild hyponatremia (serum sodium concentration $[Na]_s$ 125–134 mmol/l) can have important consequences that include a reduced performance in mental function tests, disturbances of balance, osteopenia and a high fracture risk [3], and is associated with mortality [4].

A critical question is whether correction of hyponatremia reduces mortality. Correction of hyponatremia was reported to have a beneficial effect on patient survival in one study [4] but no effect on survival in another study [5]. Large prospective studies in populations at risk (e.g., the elderly and patients with heart failure, among others) are needed to answer this question. Nevertheless, considerations other than mortality (e.g., mental status or bone status)

[1]Renal Section, Medicine Service, Raymond G. Murphy Veterans Affairs Medical Center (111C), 1501 San Pedro, SE, Albuquerque, NM 87108, USA
[2]Division of Nephrology, Department of Medicine, University of New Mexico School of Medicine, NM, USA
[3]Department of Surgery, University of New Mexico School of Medicine, NM, USA
*Author for correspondence: Tel.: +1 505 265 1711 4733; Fax: +1 505 256 6442; antonios.tzamaloukas@va.gov

Future Medicine part of fsg

make correction of hyponatremia a compelling therapeutic goal.

For hyponatremia with prominent neurological manifestations or when $[Na]_s$ is ≤125 mmol/l, the recommended rate of correction of $[Na]_s$ is 4–6 mmol/l per 24 h to prevent the development of osmotic demyelination [6]. However, a higher initial rate of correction may be required if the neurological symptoms are life-threatening [7]. Two therapeutic developments, seemingly diametrically opposite on cursory examination, have taken place recently.

The first development was the introduction of vasopressin V_2 receptor antagonists (vaptans) [8]. The reversal of the effect of vasopressin on urinary concentration by vaptans promotes free water excretion (dilute urine) and correction of hyponatremia. By contrast, vasopressin infusion, which was proposed as a safe and effective treatment for all severe hyponatremias treated with simultaneous hypertonic saline infusion [9], results in urine concentration.

The availability of two treatments with opposite effects on water excretion by the kidneys places emphasis on the clarification of the indications and risks of these treatments. A proper diagnosis of hyponatremia should address three issues:

- Is the hyponatremia acute or chronic?
- Is it hypovolemic, euvolemic or hypervolemic?
- Is the urine concentrated, indicating high serum levels of vasopressin (as is the case in most instances of hyponatremia), or dilute (e.g., in several psychiatric disorders, chronic renal failure or poor availability of solutes requiring excretion by the kidneys)?

The two methods of treatment have not been evaluated in all types of hyponatremia. It appears appropriate, for now, to consider vaptans as contraindicated in hyponatremias treated with infusion of hypertonic or isotonic saline [7] or those accompanied by dilute urine. The clear indication for use of desmopressin infusion, along with saline infusion, to prevent rapid correction of hyponatremia is in the management of hypovolemic hyponatremia and hyponatremia associated with dilute urine.

Future developments in the management of hyponatremia could be beneficial in four areas. The first is bedside determination of body water. The calculation of the volume of saline needed to produce a desired rise in $[Na]_s$ requires an estimate of body water. There is a compelling need for the use of more accurate estimates of body water in the calculation of the required volume of saline. Currently available formulas for estimating body water, based on sex, age, weight and height, were derived in euvolemic states and are inaccurate in hypovolemic or hypervolemic states [7].

Monitoring urine volume is the only point-of-care measurement currently available in most hospitals. The development of bedside methods allowing repeated and rapid measurement of $[Na]_s$, serum vasopressin levels, and urine sodium and potassium concentration is the second area of research that could improve the management of severe hyponatremia. Monitoring the effects of the treatment of hyponatremia would be improved by this research. Third, genomic studies identifying new mutations in the vasopressin receptor aquaporin 2 functional axis would not only improve therapeutic measures, for example, in guiding the use of vaptans or vasopressin, but also lead to a better understanding of the details of the mechanism of urinary concentration. An activating mutation of the V_2 receptor, leading to immeasurable (very low) serum vasopressin levels, high urine osmolality levels and hyponatremia, has been described [8]. It is unlikely that vasopressin or vaptans will be effective in this setting. Fourth, studies aimed at unraveling the molecular and biochemical mechanisms of the osmotic demyelination syndrome could lead to the discovery of therapies for preventing this syndrome [10].

Recent epidemiological studies evaluated the frequency of hypernatremia in outpatient and hospitalized populations and its association with mortality. An association between hypernatremia and osmotic demyelination has also been described. We found no new developments in the treatment of hypernatremia.

Abnormalities in serum potassium concentration

While hyperkalemia and hypokalemia are uncommon, as determined by outpatient blood testing of the general population [1], their frequencies are higher in susceptible patient populations and their adverse effects on the survival of these populations are manifested even at modest deviations of serum potassium concentration ($[K]_s$) from the normal range [11,12]. It has long been recognized that evaluation of abnormal $[K]_s$ values begins with a detailed investigation

of both the external potassium balance (intake and output) and the internal balance (exchanges between the intracellular and extracellular compartments). Recent progress has been made in the epidemiological and therapeutic aspects of hyperkalemia and in the mechanisms of defense of $[K]_s$. The management of hypokalemia has not changed recently. The remaining of this section will be devoted to hyperkalemia.

The therapeutic effectiveness of medications blocking the renin–angiotensin-2–aldosterone axis in vulnerable populations, including primarily patients with congestive heart failure and proteinuric chronic kidney disease, has expanded the use of these medications. However, such therapies have led to an increased prevalence of hyperkalemia [13]. Active surveillance of $[K]_s$ and aggressive prevention of hyperkalemia are required in patients taking these drugs. While dietary restriction of potassium intake and diuretics that promote kaliuresis are important measures for preventing hyperkalemia, they are not always sufficient. Medications binding potassium in the GI tract are often needed.

While polystyrene sulfonate preparations, with or without sorbitol, have been the mainstay of treatment and prevention of hyperkalemia for six decades, they have been strongly criticized as of late because of gastrointestinal toxicity [14]. Patiromer (RLY506) is a new nonabsorbable cation-exchange polymer that is being evaluated as an oral agent for the treatment and prevention of hyperkalemia. Early reports suggest that this compound is effective and well tolerated [15]. Studies of longer duration and in various patient groups will determine whether the early optimism regarding this compound is justified.

Future developments that address the following four areas have the capacity to improve the management of problems related to potassium homeostasis:

- Investigation of the structure and function of colonic potassium channels [16]. This research could lead to both new insights in the regulation of potassium homeostasis and novel drugs that promote the elimination of potassium through the GI tract;
- Characterization of phenotypes of mineralocorticoid receptors in epithelial cells. These phenotypes affect the development of hyperkalemia by the use of medications blocking the binding of aldosterone to its receptors [17]. Further work in this area is expected to lead to personalized medicine informed by the genotype of each patient [18];
- Elucidation of the stereochemical structure and function of the potassium channels in cell membranes, as well as the genotypes of these channels and their effects on potassium transport and the compounds affecting transport through these channels [19]. This research should lead to better understanding of the internal potassium balance, which is a critical area of incomplete and imprecise knowledge, and will provide the means to use this balance in the prevention of abnormalities in potassium homeostasis;
- Identification of the biochemical compounds and steps involved in the process of feed-forward regulation of $[K]_s$. The feed-forward concept refers to regulation of $[K]_s$ through signaling molecules that sense the movement of potassium across vessel walls or epithelia. These molecules are located strategically, for example in the wall of the gut to detect potassium absorption after a meal, or in the vessels of muscles to detect egress of potassium from muscle cells during exercise, and activate effector mechanisms stimulating potassium uptake by cells and excretion through the kidneys [20].

Elucidation of the chemistry and function of the molecules that are involved in the feed-forward process could lead to new therapeutic methods.

The contents of this report, particularly in areas that address future research, represent the vision of the authors. Our vision is not all-inclusive. We selected areas that are, in our opinion, likely to lead to improvements in the clinical praxis. Research in many other aspects of the metabolism of monovalent cations and its clinical implications should be encouraged.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Liamis G, Rodenburg EM, Hofman A *et al.* Electrolyte disorders in community subjects: prevalence and risk factors. *Am. J. Med.* 126(3), 256–263 (2013).

2 Vandergheynst F, Sakr Y, Felleiter P *et al.* Incidence and prognosis of dysnatraemia in critically ill patients: analysis of a large prevalence study. *Eur. J. Clin. Invest.* 43(9), 933–948 (2013).

3 Schrier RW. Does "asymptomatic" hyponatremia exist? *Nat. Rev. Nephrol.* 6(4), 185 (2010).

4 Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am. J. Med.* 122(9), 857–865 (2009).

5 Lee SE, Choi DJ, Yoon CH *et al.* KorHF Registry. Improvement of hyponatraemia during hospitalization for acute heart failure is not associated with improvement of prognosis: an analysis from the Korean Heart Failure (KorHF) registry. *Heart* 98(24), 1798–1804 (2012).

6 Sterns RH, Hix JK, Silver S. Treatment of hyponatremia. *Curr. Opin. Nephrol. Hypertens.* 19(5), 493–498 (2010).

7 Tzamaloukas AH, Malhotra D, Rosen BH *et al.* Principles of management of severe hyponatremia. *J. Am. Heart Assoc.* 2(1), e005199 (2013).

8 Jovanovich AJ, Berl T. Where vaptans do and do not fit in the treatment of hyponatremia. *Kidney Int.* 83(4), 563–567 (2013).

9 Sood L, Sterns RH, Hix JK *et al.* Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. *Am. J. Kidney Dis.* 61(4), 571–578 (2013).

10 Gankam-Kengne F, Soupart A, Pochet R, Brion JP, Decaux G. Minocycline protects against neurologic complications of rapid correction of hyponatremia. *J. Am. Soc. Nephrol.* 21(12), 2099–2108 (2010).

11 Einhorn LM, Zhan M, Hsu VD *et al.* The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch. Intern. Med.* 169(12), 1156–1162 (2009).

12 Torlen K, Kalantar-Zadeh K, Molnar MZ *et al.* Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. *Clin. J. Am. Soc. Nephrol.* 7 (8), 1372–1284 (2012).

13 Juurlink DN, Mamdani MM, Lee DS *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N. Engl. J. Med.* 351(6), 543–551 (2004).

14 Sterns RH, Rojas M, Bernstein P *et al.* Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J. Am. Soc. Nephrol.* 21(5), 733–735 (2010).

15 Buysse JM, Huang IZ, Pitt B. PEARL-HF: prevention of hyperkalemia in patients with heart failure using a novel polymeric potassium binder, RLY5016. *Future Cardiol.* 8(1), 17–28 (2012).

16 Sandle GI, Hunter M. Apical potassium (BK) channels and enhanced potassium excretion in the human colon. *QJM* 103(2), 85–89 (2010).

17 Cavallari LH, Groo VL, Viana MA *et al.* Association of aldosterone concentration and mineralocorticoid receptor phenotype with potassium response to spironolactone in patients with heart failure. *Pharmacotherapy* 30(1), 1–9 (2010).

18 Cavallari NH, Nutesku EA, Duarte JD. Personalized medicine in cardiology: the time for genotype-guided therapy is now. *Future Cardiol.* 9(4), 459–464 (2013).

19 Tao X, Avalos JL, Chen J *et al.* Crystal structure of the eukaryotic strong inward-rectifier K^+ channel Kir2.2 at 3.1 Å resolution. *Science* 326(5960), 1668–1674 (2009).

20 Young JH, McDonough AA. Recent advances in understanding integrative control of potassium homeostasis. *Annu. Rev. Physiol.* 71, 381–401 (2009).