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Diagnosis and treatment of hypernatremia

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Hypernatremia is defined as a serum sodium level above 145 mmol/L. It is a frequently encountered electrolyte disturbance in the hospital setting, with an unappreciated high mortality. Understanding hypernatremia requires a comprehension of body fluid compartments, as well as concepts of the preservation of normal body water balance. The human body maintains a normal osmolality between 280 and 295 mOsm/kg via Arginine Vasopressin (AVP), thirst, and the renal response to AVP; dysfunction of all three of these factors can cause hypernatremia. We review new developments in the pathophysiology of hypernatremia, in addition to the differential diagnosis and management of this important electrolyte disorder.

Introduction

Water balance

Hypernatremia is defined as an increase in the plasma Na^+ concentration to >145 mM. Considerably less common than hyponatremia, hypernatremia is however associated with mortality rates of as much as 40–60%. Hypernatremia most commonly occurs in ICUs, mostly developing after admission, and has been associated with increased mortality and prolonged length of ICU stay [1]. A recent study showed that severity rather than duration of the hypernatremia following the ICU admission was associated with increased mortality and increased length of stay (40% and 28% increase, respectively) [2].

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Secondary analysis of a recent prospective study in the ICU showed that almost 50% of pre-dialysis patients with acute kidney injury had a dysnatremia, mainly hypernatremia, and that there was an increase in mortality especially with severe hypernatremia (serum sodium $\geq$156) compared to normonatremic patients (89.1% versus 64.6% respectively) [3]. Preoperative hypernatremia is also associated with increased perioperative 30-day morbidity and mortality [4].

Understanding hypernatremia requires a comprehension of the main body fluid compartments as well as an appreciation of the basic concepts of maintenance of normal body water balance. Total body water (TBW) is a key physiological term in this context. TBW has been estimated to be about 60% of body weight in men and 50% in women; this notably is a simplified estimate. TBW is further divided into two main compartments, an extracellular fluid (ECF) and an intracellular fluid (ICF) compartment. The ECF compartment includes plasma, interstitial and lymph fluid, connective tissue and bone, transcellular fluid within body cavities, and adipose tissue [5].

Tonicity refers to the behavior of cell volume in a given solution and represents the action of effective osmoles across a membrane. Cellular volume expands when cells are bathed in relatively hypotonic solutions and contracts when bathed in relatively hypertonic solutions, due to movement of water in and out of the cell respectively to eventually reach a steady state tonicity. Effective or active osmoles include sodium (and associated anions) and glucose in the extracellular compartment, whereas the ionic osmotic driver in the intracellular compartment is primarily potassium (and associated anions). On the other hand, osmolality represents the sum of both effective and ineffective osmoles in any 1 kg of body fluid. Ineffective osmoles, typically urea and alcohol [6] can cross freely across cell membranes and hence do not generally alter cellular volume. Osmolality is a poor indicator of tonicity given the presence of these ineffective osmoles. While effects of tonicity on cellular size cannot be measured directly, serum sodium can serve as a useful surrogate for tonicity in all body compartments at steady state.

Hypertonicity (dehydration) refers to the loss of total-body water such that cellular volume contracts, whereas volume depletion is a term used to signify loss of extracellular fluid volume. These two distinct conditions have different clinical features as well as different therapeutic responses [6,7].

Osmoreceptors and thirst

Vasopressin secretion, thirst, and the renal response to vasopressin collaborate to maintain normal human body fluid osmolality between 280 and 295 mOsm/kg. Thirst and vasopressin secretion are under the control of osmoreceptor neurons within the central nervous system (CNS) (see Fig. 1). Classic canine experiments performed in the 1940s, correlating the effect on urine output of carotid infusion of various osmolytes, led to the postulation of a central "osmoreceptor" [8]. The primary "osmostat" within the CNS is encompassed within the *organum vasculosum* of the *lamina terminalis* (OVLT); this small periventricular region lacks a blood–brain barrier, allowing for direct sensing of the osmolality of circulating blood. Osmoreceptive neurons are however widely distributed within the CNS, such that vasopressin (AVP) release and thirst are controlled by overlapping osmosensitive neural networks [9–12]. Osmosensitive neurons are thus found in the subfornical organ (SFO) and the *nucleus tractus solitarii*, centers which help integrate regulation of circulating osmolality with that of related phenomena, such as extracellular fluid volume [9,10,12] (see Fig. 1).

Osmosensitive neurons from the supraoptic nucleus differ dramatically from hippocampal neurons, in that they demonstrate exaggerated changes in cell volume during cell shrinkage (hypertonic media) or cell swelling (hypotonic media) [13]. In hippocampal neurons, cell swelling evokes a rapid regulatory volume decrease (RVD) response, whereas cell shrinkage evokes a regulatory volume increase (RVI) response. In consequence, if external tonicity is slowly increased or decreased these RVD and RVI mechanisms are sufficient to prevent any change in the cell volume of hippocampal neurons; in contrast, osmosensitive neurons exhibit considerable changes in cell volume during such osmotic ramps [13]. This relative lack of volume regulatory mechanisms maximizes the mechanical effect of extracellular tonicity and generates an ideal osmotic sensor.

Osmosensitive neurons depolarize after cell shrinkage induced by exposure to hypertonic stimuli, with a marked increase in neuronal spike discharges; the associated current is due to activation of a nonselective cation channel [14], with five-fold higher permeability for Ca^{2+} over Na^{+} [15]. Hypotonic