Dysnatremias in Critically ill Patients

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Summary

Sodium disturbances (dysnatremias) are considered a common problem in adult patients admitted to hospital and intensive care units (ICU). In fact, the majority of these abnormalities develop after the patient is admitted to the ICU because of their incapacitation, lack of access to free water, reliance on intravenous fluid and nutritional support, and the usually serious nature of their underlying disease which often leads to impaired renal water handling, so patients in the ICU are at high risk of developing sodium disturbances.

The osmoreceptor-ADH system, the thirst mechanism and angiotensin II and aldosterone system are the main systems responsible for regulation of sodium concentration and ECF osmolarity.

Hyponatremia is defined as a serum sodium concentration of less than 135 mEq/L. The precise incidence of hyponatremia varies depending on the conditions underlying it.

Hyponatremic disorders are divided into euvolemic, hypovolemic and hypervolemic. Several causes can lead to hyponatremia the most common are: use of diuretics, extrarenal loss such as vomiting and diarrhea, SIADH and hypothyroidism.

CNS is the most affected system from hyponatremia. Symptoms may be mild in from of headache, nausea, lethargy and confusion, or may be severe in the form of hemiparesis, seizures, hallucinations, tremors, coma and even cardiac arrest.

Management of hyponatremia includes reversible of CNS symptoms by using of hypertonic saline in a slow rate to avoid harmful complications. The second step in the management is treating the underlying cause.

Hypernatremia is a disorder of water metabolism and is usually defined as a plasma sodium concentration above 145 mEq/L.

Hypernatremia is particularly common in critically ill patients, but there are no prospective data available on the prevalence of hypernatremia in intensive care unit (ICU).

The origin of hypernatremia requires several factors to develop in ICU patients such as: the administration of hypertonic sodium bicarbonate solutions; renal water loss through a concentrating defect from renal disease or the use of diuretics or solute diuresis from glucose or urea in patients on high protein feeds or in a hypercatabolic state; gastrointestinal fluid losses through nasogastric suction and lactulose administration, and water losses through fever, drainages, and open wounds. Thus, most etiologies of hypernatremia involve states of impaired water access in conjunction with excessive free water losses.

Clinical effects of hypernatremia result from plasma hyperosmolarity, leading to intracellular dehydration and decrease in cell volume, particularly in brain cells, producing shrinking of brain size. This may predispose to vascular stretching and subsequent rupture of meningeal vessels with potential risk of cerebral or subarachnoid hemorrhage and neurological deficit such as convulsions and even cardiac arrest.

Treatment of hypernatremia involve identification of underlying cause of ongoing fluid loss and replacement of fluid lost by a certain rate to prevent brain cell edema and further neurological consequences

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Introduction

Dysnatremias (hypo- and hypernatremia) are common in patients admitted to the intensive care unit (ICU) with a prevalence approaching 20–30% and they are independent risk factors for poor prognosis. Both the dysnatremia itself and the treatment of the electrolyte disturbance can be associated with morbidity and mortality making careful monitoring for and treatment of sodium disorders an imperative in the critically ill patient ***(Funk et al., 2010).***

Extracellular fluid osmolarity and sodium concentration are closely linked because sodium is the most abundant ion in the extracellular compartment. Plasma sodium concentration is normally regulated within close limits of 135 to 145 mEq/L, with an average concentration of about 140 mEq/L while osmolarity averages about 300 mOsm/L. There are multiple mechanisms that control fluid Osmolarity and sodium concentration, three primary systems are especially involved in regulating the concentration of sodium and osmolarity of extracellular fluid: (1) the osmoreceptor-ADH system, (2) the thirst mechanism and (3) angiotensin II and aldosterone system ***(Guyton and Hall, 2006)***.

Hyponatremia is the most common electrolyte disorder ***(Janicic and Verbalis, 2003),*** reported to occur in up to 6% of hospitalized patients ***(Han and Cho, 2002).*** The precise incidence of hyponatremia varies depending on the conditions underlying it and the criteria used to define it. When defined as a serum sodium concentration of less than 135 mEq/L, hyponatremia has been reported in 15% to 22% of hospitalized patients. In studies defining it as a concentration of 130 mEq/L or less, hyponatremia has been described in hospitalized patients at incidences of 1% to 4%***(Janicic and Verbalis, 2003).***

Hypernatremia is a disorder of water metabolism and is usually defined as a plasma sodium concentration above 145 mEq/L. Hypernatremia generally results from a net loss of body water relative to sodium and can occur with or without a loss or even gain in body sodium content ***(Oh and Carroll, 1992)***.

Treatment of either hypo or hypernatremia can be associated with serious complications, particularly if rapid correction is done. Therefore, slow correction is a must in the treatment (***Stelfox et al., 2008).***

Physiology of Regulation of Extracellular Fluid Osmolarity and Sodium Concentration

Extracellular fluid osmolarity and sodium concentration are closely linked because sodium is the most abundant ion in the extracellular compartment. Plasma sodium concentration is normally regulated within close limits of 135 to 145 mEq/L, with an average concentration of about 140 mEq/L while osmolarity averages about 300 mOsm/L ***(Guyton and Hall, 2006)***.

Table 1-1 summarizes total-body water balance; these are average values which are subject to considerable normal variations. There are two sources of body water gain: (1) water produced from the oxidation of organic nutrients, and (2) water ingested in liquids and food. There are four sites from which water is lost to the external environment: skin, respiratory passageways, gastrointestinal tract, and urinary tract. Menstrual flow constitutes a fifth potential source of water loss in women ***(Widmaier et al., 2003)*.**

Table 1-2 is a summary of total-body balance for sodium chloride. The excretion of sodium and chloride via the skin and gastrointestinal tract is normally small but increases markedly during severe sweating, vomiting, or diarrhea. Hemorrhage can also result in loss of large quantities of both salt and water ***(Widmaier et al., 2003)*.**

Table 1-1 Average daily water gain and Loss in adults(Widmaier et al.,2003)

Intake	
In liquids	1200 ml
In food	1000 ml
Metabolically produced	350 ml
Total	**2550 ml**
Output	
Insensible loss(skin and lungs)	900 ml
Sweat	50 ml
In feces	100 ml
Urine	1500 ml
Total	**2550 ml**

Table 1-2 Daily sodium chloride intake and loss(Widmaier et al.,2003)

Intake	
Food	**15.50 g**
Output	
Sweat	0 .25 g
Feces	0.25 g
Urine	10.50 g
Total	**10.50 g**

In most clinical laboratories, plasma osmolarity is not routinely measured. However, because sodium and its associated anions account for about 94 per cent of the solute in the extracellular compartment, plasma osmolarity (P_{osm}) can be roughly approximated as:

P_{osm} = 2.1 × Plasma sodium concentration.

So with a plasma sodium concentration of 140 mEq/L, the plasma Osmolarity would be estimated from the formula above to be about 298 mOsm/L ***(Guyton and Hall, 2006)***.

Control of sodium ion concentration and Osmolarity

There are multiple mechanisms that control the amount of sodium and water excretion by the kidneys, three primary systems are especially involved in regulating the concentration of sodium and Osmolarity of extracellular fluid: (1) the osmoreceptor-ADH system, (2) the thirst mechanism and (3) Angiotensin II and Aldosterone system ***(Guyton and Hall, 2006)***.

(1) Osmoreceptor-ADH Feedback System:

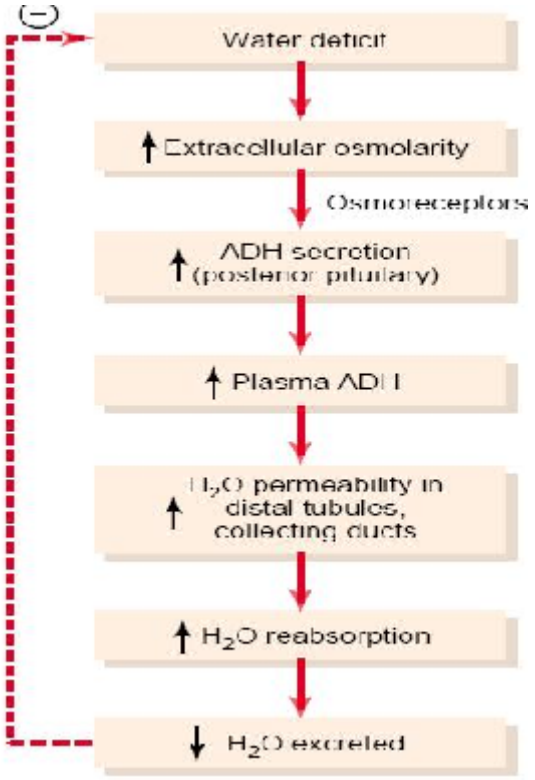
A decreased extracellular volume as in diarrhea or hemorrhage, elicits an increased in ADH (vasopressin) secretion, this increased vasopressin increases the water permeability of the collecting ducts. More water is reabsorbed and less is excreted, and so water is retained to help stabilize the extracellular volume ***(Widmaier et al., 2003)*.**

*This feedback system operates as follows:

An increase in extracellular fluid osmolarity causes the special nerve cells called ***osmoreceptor cells***, located in the *anterior hypothalamus* near the supraoptic nuclei, to shrink. Shrinkage of the osmoreceptor cells causes them to fire, sending nerve signals to additional nerve cells in the supraoptic nuclei, which then relay these signals down the stalk of the pituitary gland to the posterior pituitary. These action potentials conducted to the posterior pituitary stimulate the release of ADH, which is stored in secretory granules in the nerve endings; the released ADH enters the blood stream and is transported to the kidneys, where it increases the water permeability of the late distal tubules, cortical collecting tubules, and medullary collecting ducts. This in turn causes increased water reabsorption and excretion of a small volume of concentrated urine. Thus, water is conserved in the body while sodium and other solutes continue to be excreted in urine; this

causes dilution of the solutes in the extracellular fluid and leads to return of the extracellular osmolarity back to normal ***(Stricker and Sved, 2002)***

Figure (1-1) shows this feedback.



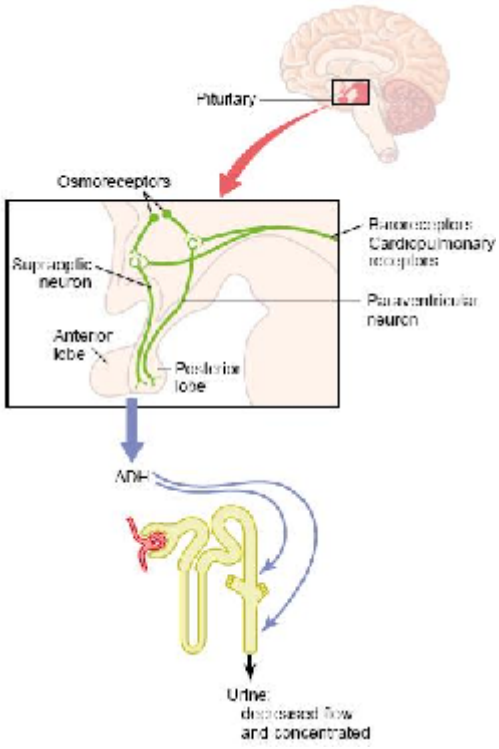


Figure (1-1): Osmoreceptor-ADH feedback ***(Quoted from Guyton and Hall, 2006)***

Figure (1-2): Neuroanatomy of Hypothalamus and posterior pituitary where ADH synthesis and release occur ***(Quoted from Guyton and Hall,*** **2006)**

<u>*ADH Synthesis in Supraoptic and Paraventricular Nuclei of the Hypothalamus and ADH Release from the Posterior Pituitary:</u>

As shown in figure (1-2), The hypothalamus contains two types of agnocellular (large) neurons that synthesize ADH in the supraoptic and paraventricular nuclei of the hypothalamus, about five sixths in the supraoptic nuclei and about one sixth in the paraventricular nuclei. Both of these nuclei have axonal extensions to the posterior pituitary. Once ADH is synthesized, it is transported down the axons of the neurons to their tips, terminating in the posterior pituitary gland. When the supraoptic and paraventricular nuclei are stimulated by increased osmolarity or other factors, nerve impulses pass down these nerve endings, changing their membrane permeability and increasing calcium entry. ADH stored in the secretory granules (also called vesicles) of the nerve endings is released in response to increased calcium entry. The released ADH is then carried away in the capillary blood of the posterior pituitary into the systemic circulation ***(Guyton and Hall, 2006)***.

A second neuronal area important in controlling osmolarity and ADH secretion is located along the *anteroventral region of the third ventricle*, called the *AV3V region*. At the upper part of this region is a structure called the *subfornical organ*, and at the inferior part is another structure called the *organum vasculosum* of the *lamina terminals*. Between these two organs is the *median preoptic nucleus,* which has multiple nerve connections with the two organs as well as with the supraoptic nuclei and the blood pressure control centers in the medulla of the brain. Lesions of the AV3V region cause multiple deficits in the control of ADH secretion, thirst, sodium appetite, and blood pressure. Electrical stimulation of this region or stimulation by angiotensin II can alter ADH secretion, thirst, and sodium appetite ***(Stricker and Sved, 2002)***

*Regulation of ADH releases into the circulation:

Table (1-3) summarizes the regulation of ADH release

Table(1-3)	**Regulation of ADH Secretion *(Guyton and Hall, 2006)*.**

Increase ADH	**Decrease ADH**
↑plasma Osmolarity	↓plasma Osmolarity
↓Blood volume	↑Blood volume
↓Blood pressure	↑Blood pressure
Nausea	
Hypoxia	
Drugs:	**Drugs:**
Morphine	Alcohol
Nicotine	Clonidine
Cyclophosphamide	Haloperidol

ADH release is also controlled by cardiovascular reflexes that respond to decreases in blood pressure and/or blood volume, including (1) the *arterial baroreceptors reflexes* and (2) *the cardiopulmonary reflexes*, these reflex pathways originate in high-pressure regions of the circulation, such as the aortic arch and carotid sinus, and in the low-pressure regions, especially in the cardiac atria. Afferent stimuli are carried by the vagus and glossopharyngeal nerves with synapses in the nuclei of the tractus solitarius. Projections from these nuclei relay signals to the hypothalamic nuclei that control ADH synthesis and secretion. Thus, in addition to increased osmolarity, two other stimuli increase

ADH secretion: (1) decreased arterial pressure and (2) decreased blood volume ***(Stricker and Sved, 2002)***

*Mechanism of action of ADH:

Several types of vasopressin receptors exists such as V1a (causing vasoconstriction, platelet aggregation, inotropic stimulation, myocardial protein synthesis), V1b (causing secretion of adrenocorticotropic hormone), and V2 (causing water reabsorption and release of von Willebrand factor and factor VIII) ***(Chirag et al., 2010).***

The mechanism by which vasopressin exerts its antidiuretic effect is activated by **V_2 receptors** and involves the insertion of proteins called water channels into the apical (luminal) membranes of the principal cells of the collecting ducts. Movement of water across membranes by simple diffusion is now known to be augmented by movement through water channels called **aquaporins** (AQP)**,** and to date 13 aquaporins (AQP0–AQP12) have been identified and water channels are now known to be expressed in almost all tissues in the body. The vasopressin-responsive water channel in the collecting ducts is aquaporin-2. These channels are stored in endosomes inside the cells, and vasopressin causes their rapid translocation to the luminal membranes ***(Barret et al., 2010).***

V_{1A} receptors mediate the vasoconstrictor effect of vasopressin which is a potent stimulator of vascular smooth muscle in vitro. However, relatively large amounts of vasopressin are needed to raise blood pressure in vivo, because vasopressin also acts on the brain to cause a decrease in cardiac output. The site of this action is the area postrema, one of the circumventricular organs. The **V_{1B} receptors** (also called **V_3 receptors**) appear to be unique to the anterior pituitary, where they mediate increased adrenocorticotropic hormone (ACTH) secretion from the corticotropes ***(Barret et al., 2010).***

(2) The thirst mechanism:

Thirst is defined as the conscious desire for water; the kidneys minimize fluid loss during water deficits through the osmoreceptor-ADH feedback system. Adequate fluid intake, however, is necessary to counterbalance whatever fluid loss does occur through sweating and breathing and through the gastrointestinal tract. Fluid intake is regulated by the thirst mechanism, which, together with the osmoreceptor-ADH mechanism, maintains precise control of extracellular fluid osmolarity and sodium concentration ***(McKinley and Johnson, 2004)***.

*Central Nervous System Centers for Thirst

As seen in figure (1-2), the same area along the anteroventral wall of the third ventricle that promotes ADH release also stimulates thirst. Located anterolaterally in the preoptic nucleus is another small area that, when stimulated electrically, causes immediate drinking that continues as long as the stimulation lasts. All these areas together are called the ***thirst center***, the neurons of the thirst center respond to injections of hypertonic salt solutions by stimulating drinking behavior. These cells almost certainly function as osmoreceptors to activate the thirst mechanism, in the same way that the osmoreceptors stimulate ADH release ***(McKinley and Johnson, 2004)***

*Stimuli for Thirst:

As shown in figure (1-3), the subjective feeling of thirst is stimulated both by a lower extracellular volume and a higher plasma osmolarity, the latter being the single most important stimulus under normal physiological conditions. These are precisely the same two changes that stimulate vasopressin production and the osmoreceptors and baroreceptors that control vasopressin secretion are the same as those for thirst ***(Widmaier et al., 2003).***

A third important stimulus for thirst is angiotensin II. Studies in animals have shown that angiotensin II acts on the subfornical organ and on the organum vasculosum of the lamina terminals. These regions are outside the blood-brain barrier, and peptides such as angiotensin II diffuse into the tissues ***(McKinley and Johnson, 2004)*** Thus, the renin-angiotensin system may help regulate not only sodium balance but water balance as well and constitutes one of the pathways by which thirst is stimulated when extracellular volume is decreased ***(Widmaier et al., 2003).***

Dryness of the mouth and mucous membranes of the esophagus can elicit the sensation of thirst. As a result, a thirsty person may receive relief from thirst almost immediately after drinking water, even though the water has not been absorbed from the gastrointestinal tract and has not yet had an effect on extracellular fluid osmolarity ***(McKinley and Johnson, 2004)***

The ability of animals and humans to “meter” fluid intake is important because it prevents overhydration. After a person drinks water, 30 to 60 minutes may be required for the water to be reabsorbed and distributed throughout the body. If the thirst sensation were not temporarily relieved after drinking water, the person would continue to

drink more and more, eventually leading to overhydration and excess dilution of the body fluids ***(Guyton and Hall, 2006)***.

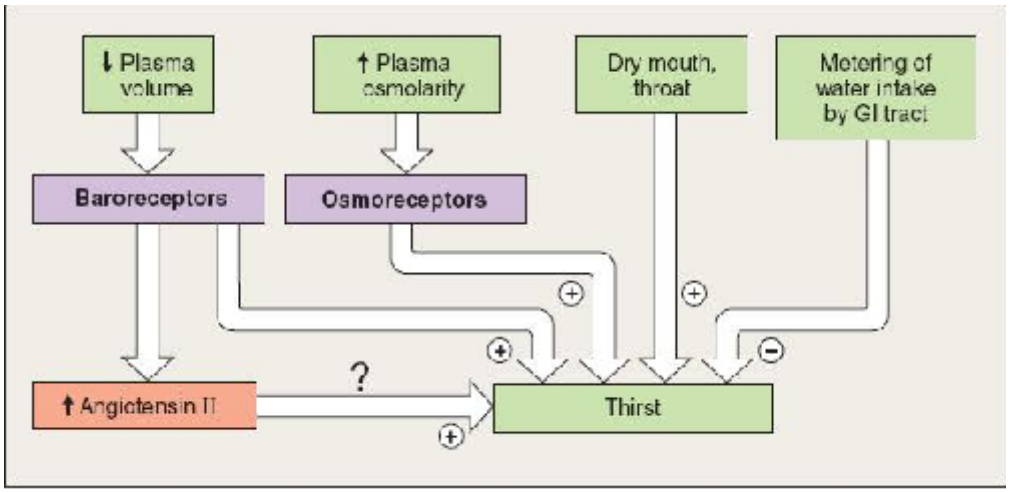


Figure (1-3): stimulus for thirst (*Quoted from Widmaier et al., 2003)*

*Threshold for Osmolar Stimulus of Drinking:

The kidneys must continually excrete at least some fluid, even in a dehydrated person, to rid the body of excess solutes that are ingested or produced by metabolism. Water is also lost by evaporation from the lungs and the gastrointestinal tract and by evaporation and sweating from the skin. Therefore, there is always a tendency for dehydration, with resultant increased extracellular fluid sodium concentration and osmolarity. When the sodium concentration increases only about 2 mEq/L above normal, the thirst mechanism is activated, causing a desire to drink water. This is called the **threshold for drinking**. Thus, even small increases in plasma osmolarity are normally followed by water intake, which restores extracellular fluid osmolarity and volume towards normal. In this way, the extracellular fluid osmolarity and sodium concentration are precisely controlled ***(Guyton and Hall, 2006)***.

*Integrated Responses of Osmoreceptor-ADH and Thirst Mechanisms in Controlling Extracellular Fluid Osmolarity and Sodium Concentration:

In a healthy person, the osmoreceptor-ADH and thirst mechanisms work in parallel to precisely regulate extracellular fluid osmolarity and sodium concentration, despite the constant challenges of dehydration. When either the ADH or the thirst mechanism fails, the other can ordinarily still control extracellular osmolarity and sodium concentration with reasonable effectiveness, as long as there is enough