Sodium

EM Semenya iD

Department of Anaesthesia, School of Clinical Medicine, Faculty of Health Sciences, Helen Joseph Hospital, University of the Witwatersrand, South Africa
Corresponding author, email: elizabeth.semenya@wits.ac.za

Sodium is a major extracellular cation. It is a significant determinant of the osmolality of the plasma. Human cells are bathed in salty water, so the osmolality must be regulated. The primary cause of dysnatraemias (abnormal sodium concentrations), hyper- and hypo-, is caused by the imbalance of electrolyte-free fluid intake and loss.[1] Clinicians must look at correcting the fluid abnormality instead of focusing on serum sodium. Dysnatraemias are a significant cause of morbidity in intensive care unit (ICU) patients, with an incidence of up to 27% in ICU patients compared to 0.2% in general ward patients.[2,3]

Keywords: sodium, extracellular cation, osmolality

Relationship of plasma sodium, electrolytes, and water content

Osmolality is the concentration of osmoles dissolved per kilogram of plasma water. Osmolarity is the concentration of osmoles per litre of plasma water. Osmolality is the preferred term since it can be measured with an osmometer.[1] Tonicity is the concentration of moles (effective osmoles) that do not cross cell membranes.[1] The accumulation of effective osmoles drives the movement of water. Therefore, hypotonic plasma drives water movement intracellularly, causing the cells to swell, while hypertonicity drives water out of the cells, causing them to shrink.[1,4]

Sodium and glucose, in the absence of insulin, act as effective osmoles and contribute to both osmolality and tonicity.[1] Since it permeates membranes, urea contributes to osmolality without affecting tonicity.[1] Therefore, the extracellular fluid regulates the body's solute and sodium. The body has mechanisms to maintain the tonicity of the plasma close to an acceptable level. The regulatory mechanism keeps the sodium level within its normal range (135–145 mmol/L).

The solute content in extracellular and intracellular is the same. The difference in osmolality between intracellular and extracellular is the same. Aquaporins on cellular membranes allow the free movement of water to balance osmolality, while the Na+/K+ ATPase keeps the sodium outside the cells. Though sodium is extracellular, and potassium is an intracellular cation, body fluid can be considered a large bath containing sodium, potassium, and water. Edelman's equation expressed this relationship: Plasma sodium is directly proportional to the sum of exchangeable sodium and potassium and inversely proportional to extracellular fluid.[4,5]

A substantial amount of sodium is bound to proteoglycan, the building block of connective tissue, cartilage, and bone.[5] The concentration of sodium in cartilage is twice that of plasma. This high sodium concentration allows the cartilage to hold water and withstand pressures exceeding 20,000 mmHg during exercise.[5,6]

Proteoglycan in the skin is a sodium reservoir, and the number of negative charges on its surface is related to the sodium concentration in the interstitial fluid.[5] In rat experiments, rats with chronic hyponatraemia experienced osteopenia more than those with vitamin D deficiency.[5] Sodium loss from the bone exceeded the calcium loss.[5] Osteoclast activity increases from the direct sodium effect and possibly vasopressin.[5] In humans, chronic hyponatraemia causes osteoporosis and recurrent fractures.[1,5] During extreme endurance exercises, bone density decreases remarkably due to changes in plasma sodium resulting from the nonosmotic release of antidiuretic hormone (ADH) from pain and stress and the resultant hyponatraemia.[1,5]

Plasma sodium concentration and tonicity balance

Plasma sodium and blood-brain barrier

Sodium readily crosses the systemic endothelial membrane through the clefts between endothelial cells, resulting in a similar sodium concentration between the plasma and the interstitial fluids.[1,5] There is a slight difference attributed to the concentration of albumin. However, the brain has tight endothelial junctions lined by astrocytic foot processes, creating a blood-brain barrier, thereby preventing sodium from crossing the barrier. Abnormal plasma sodium causes water to enter or leave the brain, leading to swelling or shrinkage of the brain.[5]

Regulation of plasma sodium and extracellular fluid osmolarity

A feedback system regulates the plasma osmolality and sodium concentration. When the osmolality of body fluid is high, the volume receptors are responsible for thirst and ADH secretion.[1,5] The true osmoreceptors are hypothalamic neurons expressing transient receptor potential cation channel subfamily vanilloid

member 1 and member 4 (TRPV1 and TRPV4). TRPV1 responds to capsaicin, a vanilloid which results in a burning sensation associated with ingesting chillies.[5] The polymorphism of TRPV4 has been identified in humans in average ageing men and can result in mild hyponatraemia compared to those without the polymorphism.[5] The ADH is synthesised in the hypothalamus as a prohormone, thereafter cleaved and stored as ADH in the posterior pituitary.[1] Hypertonicity causes shrinkage of the osmoreceptors, which causes subsequent depolarisation and release of ADH from the posterior pituitary.[1]

Healthy individuals' thirst and vasopressin secretion are suppressed when sodium concentrations are below 135 mmol/L, while it continues to rise with increasing sodium levels above 135 mmol/L.[5] It may also be secreted in response to circulatory inadequateness (hypovolemia), inappropriately like in the syndrome of inappropriate ADH secretion (SIADH), and can be secreted ectopically with no haemodynamic stimulus or osmotic stimulus.[1,5,7]

Renal action of antidiuretic hormone

The site of action of the ADH is the renal collecting ducts, where it exerts its effects by binding onto the V2 receptors in the collecting ducts.[1,5] Without ADH, the collecting ducts are impervious to water, producing dilute urine.[1,5] Once ADH is bound, the aquaporins are inserted into the collecting ducts, allowing the water to seep towards the hypertonic renal medulla.[1] When the sodium concentration is 145 mmol/L, the level of vasopressin is highest, producing maximally concentrated urine of about 1 200 mOsm per kilogram.[1,5] The presence of dilute urine in the face of high sodium indicates vasopressin deficiency, nephrogenic or neurogenic diabetes insipidus.[5,6] In the conscious patient with a total deficiency of vasopressin or resistance of the renal tubules to respond to the effects of vasopressin, hypernatraemia doesn't develop because the thirst mechanism remains intact.[1,5,6] Hypernatraemia only develops in patients who are too sick, unconscious, young, or old.[2,5,8]

Maximal dilution of urine also prevents hyponatraemia, except if water intake is excessive.[1] Hypotonic hyponatraemia occurs when there is a problem in the renal tubules to produce dilute urine, as in patients taking diuretics.[1,5,7] By inhibiting sodium reabsorption in the loop of Henle, loop diuretics reduce renal medullary hypertonicity and hence reduce water reabsorption in the collecting ducts.[1] Compared to thiazide diuretics, they reduce renal concentrating ability and can contribute to hypernatraemia.[1]

Hyponatraemia

The severity of symptoms depends on the rate of onset. Hyponatraemia is a sodium concentration less than 135 mmol/L, and severe hyponatraemia is below 120 mmol/L.[1,2,5,7] Hyponatraemia can occur at low, normal, or elevated tonicity. The cells swell up as hyponatraemia develops. The brain experiences more significant stress in a fixed cranium.[1,5] Hypotonicity can lead to cell membrane rupture from swelling.

With time, cells adapt and protect their survival by adjusting their intracellular content.[1,5] Organic osmolytes are intracellular molecules like taurine, glutamate, and myo-inositol found naturally in cells.[5] With hypotonicity, they are released from the cells through volume-leak pathways.[1,5]

The symptoms are limited to the brain, though all cells are affected by hyponatraemia. Severe and permanent neurologic fallout may occur.[1,3,5,7] Astrocytes are more sensitive to the osmotic stress.[1,5] To mitigate the swelling from hypotonicity, the expulsion of potassium and other electrolytes occurs over 6–12 hours, and the organic osmoles over 24–48 hours.[1,5]

Acute hyponatraemia of fewer than 48 hours, meaning the cells did not have time to adjust as above, is uncommon.[1] There are a few cases of acute hyponatraemia, like ingestion of salt as a suicide attempt, following strenuous physical exercise, and ingestion of 3,4-methylenedioxymethamphetamine (MDMA).[1] All other cases must be treated as chronic hyponatraemia.[1,5]

The symptoms progress from mild nausea, vomiting, and headaches to severe symptoms like seizures, coma, cerebral oedema, and neurogenic pulmonary oedema.[1,5,7] Caution must be applied while correcting hyponatraemia. The foot processes of astrocytes, which encircle the neurons and capillaries, express aquaporins that allow the water to cross the blood-brain barrier.[5] Cell-cell transfer of taurine allows neuronal cells to maintain their volume while astrocytes swell up.[5] After 24–48 hours, through the loss of organic osmoles, astrocytes retain their volume but are vulnerable to the hypertonic stress associated with acute sodium replacement.[5] The astrocytes take a week to regain their organic osmoles.[5] Hypertonicity at this stage caused by rapid correction can damage astrocytes, triggering apoptosis, disruption of the blood-brain barrier, and demyelination.[1,5]

Pseudohyponatraemia is due to laboratory error in the measurement of sodium in the presence of high lipids and paraproteins. In this situation, hyponatraemia will be accompanied by normal osmolality.[1,7]

Hyponatraemia with high osmolality is seen in the presence of hyperglycaemia. The glucose draws the water from the cells into the extracellular space due to the high osmolality. This is called translocational hyponatraemia.[1,7] Sodium decreases by about 1.6 mEq/L for every 100 mg/dl increase in glucose.[1,7]

Hypotonic hyponatraemia requires investigations to find the cause, as discussed below.

Hyponatraemia and urinary dilution

Hyponatraemia and low urinary osmolality of less than 100 mOsm/kg of water indicate maximally suppressed ADH, which is the expected response.[1,5,7] The problem may indicate the administration of electrolyte-free water, which exceeds the renal excretion of water.[5] In a standard Western diet, a solute load of about 800 mOsm is generated and excreted daily. If urine can be maximally diluted to 50 mOsm/kg of water, this corresponds to clearance of 16 L electrolyte-free water.[1,5] Hyponatraemia in

this scenario may occur from primary polydipsia, ingesting less solute load like tea and toast, or excessive beer drinking.[1,5,7]

The most typical cause of hypotonic hyponatraemia is ADH deficiency, which results in the inability to dilute the urine.[1,5] The patient may be euvolemic (common cause SIADH), hypovolemic (e.g. haemorrhage and mineralocorticoid deficiency), and hypervolemic (e.g. cardiac and liver failure).[1,5,7]

Treatment of hypotonic hyponatraemia

The most significant risk in treating hypotonic hyponatraemia is an osmotic demyelinating syndrome (ODS), when sodium is replaced rapidly in chronic hyponatraemia.[1,5] The risk of ODS in acute hyponatraemia is negligible since the brain has not adjusted to low sodium.[1]

Chronic hyponatraemia with a sodium concentration of less than 105 mEq/L is associated with alcoholism, and cirrhosis carries a higher risk of ODS.[1] Hypokalaemia may increase the risk of ODS as potassium is exchanged for sodium.[5]

Acute hyponatraemia may be corrected quickly using hypertonic saline over 4–6 hours. Thereafter, 1–2 ml/kg/hour boluses to increase the sodium concentration by 4–6 ml.[1,5] In chronic severe hyponatraemia, the aim is to increase sodium by 8 mEq/L in 24 hours in the presence of severe symptoms like seizures; hypertonic saline boluses can be given as above to abolish the seizures and desmopressin can be considered at the dose of 2 mcg every 4–6 hours.[1,5,7] If the patient has mild to moderate symptoms, the aim is to increase sodium by 10–12 mEq/L over 24 hours.[1,6] With mild to moderate cases, treatment should be according to underlying conditions.

Pharmacological treatment with vaptans, an ADH antagonist, can treat euvolemic and hypervolemic hyponatraemia.[5,7]

Hypernatraemia is defined as a sodium concentration greater than 145 mmol/L. Using the Edelman equation, it can occur due to additional sodium added or the loss of extracellular fluid. It is always associated with hypertonicity.[2,5,7] Water loss is the common cause. Small increases in tonicity stimulate ADH secretion and the thirst mechanism.[1,5,7] The patients at risk are those of advanced age with reduced levels of consciousness and infirmity.[7,8]

Most patients admitted to the hospital with hypernatraemia were the elderly from old age homes, and the causes ranged from physical disabilities, which limited their ability to access water, and urinary incontinence, which made them limit their fluid intake.[1,8] Most old people are on polypharmacy, including diuretics, which may increase renal losses, and they have a reduced thirst mechanism compared to younger people.[8] hormonal changes can contribute to hypernatraemia, such as reduced renin-angiotensin-aldosterone system (RAAS), reduced aldosterone, reduced ADH, and increased atrial natriuretic peptide (ANP).[8]

An unusual cause is a tumour in the hypothalamus, leading to the inability to perceive thirst; this is called primary hypernatraemia.[1]

Causes are divided into:[1,7]

- Inadequate water intake: intubated, elderly, and reduced levels of consciousness.
- Extrarenal hypotonic losses: gastrointestinal tract (GIT) losses and sweat.
- Renal concentrating abilities: loop and osmotic diuretics and central and nephrogenic diabetes insipidus.
- Excessive salt intake: hypertonic fluid administration, like hypertonic saline, and total parenteral nutrition (TPN).

Treatment

Treat the underlying causes like diarrhoea or long-term desmopressin administration for central diabetes insipidus.

There is no consensus on the correction rate of hypernatraemia like in hyponatraemia.[1,5] Acute onset can be corrected rapidly within 24 hours. For chronic hypernatraemia, it is suggested to reduce sodium by about 0.5–1 mEq/L every hour with the aim of correcting sodium in 48 hours.[1,5,7]

Conclusion

Abnormal sodium concentration can lead to morbidity and mortality. The neurons are affected more than other cells, with mild or severe symptoms depending on the sodium level. The correction must also be carried out cautiously, as rapid correction may cause more harm than good.

ORCID

EM Semenya https://orcid.org/0009-0003-8067-8670

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