Hyper- and Hyponatraemia

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These notes have not been peer reviewed. Please refer to appropriate text books and journal articles.

Sodium and water are inextricably linked in the human body. Disorders in their homeostasis often occur in tandem and are ubiquitous. Hyponatraemia and hypernatraemia are common findings in the inpatient and outpatient settings. They are associated with an increased risk of morbidity and mortality. Sodium is the most common cation in the extracellular fluid. Normal concentration of Sodium ranges 135 mmol/l to 145 mmol/l Hypernatraemia is defined as sodium greater than 145 mmol/ whilst Hyponatraemia is defined as a sodium of less than 135 mmol/l. To understand the pathophysiology of hyper and hyponatraemia, it is important to have a knowledge of the regulation of both water and sodium by the body.

Physiology of water and sodium

Water

Total body water varies with gender, age, total body fat and hormonal status. In a normal adult male, water constitutes 60% of total body weight [TBW]. [Correction factors to estimate water volume as % of TBW: New-born 80%; Infant 70%; Paediatric 60%; Male, adult 60%; Female, adult 50%; Male, elderly 50%; Female, elderly 45%]. In adults, fluid is distributed intracellular fluid 40% of TBW and extracellular fluid 20%TBW [i.e. Intracellular water 2/3 total body water and extracellular fluid 1/3 total body water]. Most of the extracellular fluid (ECF) is found in the interstitial space i.e. 13% of TBW and 7% of TBW is found in the circulation (blood and plasma). In neonates because of a smaller mass 55% is found in the ECF.

Water generally diffuses freely across the cell membrane. The movement of water across the membrane is governed by the number of osmotically active particles on either side of the membrane (Osmolarity mmol/l, osmolality mmol/kg). Fluid flows from a low to a high osmolality until equilibrium is reached. The pressure required to prevent the movement of fluid from one side to the other across a membrane is the osmotic pressure. In the extracellular compartment sodium (Na\(^+\)), chloride (Cl\(-\)), glucose and are the major osmotically active particles. The osmolality can be calculated using a simple equation 2[Na\(^+\)] +[2K\(^+\)] + glucose + urea. Sodium is the most important determinant of ECF volume. Urea and other small molecules such as ethanol distribute rapidly and evenly across the membrane so while they contribute to osmolality they do not affect the movement of water. The effective osmolality [or tonicity] is thus 2[Na\(^+\)] +[2K\(^+\)] + glucose. The osmolality is more accurately measured in the laboratory using a technique that measures either the depression of the freezing point or boiling point of water. The normal osmolality is about 280 - 290 mosmol/l. To determine the effective osmolality urea must be subtracted from the measured value.

Both water and electrolytes move easily across the capillary membrane whilst only water moves freely across the cell membrane in the short term.

Regulation of osmolality is predominantly based on the hypothalamus monitoring and adjusting plasma osmolality via the secretion of antidiuretic Arginine vasopressin (AVP) (antidiuretic hormone (ADH)) which reduces renal water excretion. AVP binds to the V2-receptor in the collecting duct. This promotes movement of aquaporin 2 to the apical membrane and passive water reabsorption to the hypertonic medullary interstitium. If osmolality increases by a small amount, AVP is secreted to retain body water and lower serum osmolality. (An increase in osmolality will also increase a sense of thirst and increase water intake). Conversely, if a patient’s osmolality falls, AVP secretion is inhibited and free water is excreted to raise serum osmolality.

Vasopressin secretion is stimulated when plasma [Na\(^+\)] increases. Vasopressin release can also be stimulated by a reduced effective circulating volume via low pressure atrial stretch receptors, stress,
pain, nausea, vomiting, pregnancy, drugs (Isoproterenol Nitroprusside Acetaminophen Beta-2
agonists, Chlorpropamide, Clofibrate, Cyclophosphamide, Epinephrine, Lithium, Morphine (high dose),
Nicotine, NSAIDs, Prostaglandins, Tricyclic Antidepressants, Vincristine), Acetylcholine Angiotensin II,
Bradykinin and exercise. Vasopressin may be reduced by atrial tachycardia, left atrial distension,
Norepinephrine, swallowing and drugs (Alpha-adrenergic agonists, Carbamazepine, Clonidine,
Ethanol, Glucocorticoids, Morphine (low dose), Phenytoin, Promethazine).

Volume is regulated most importantly by the stimulation of the renin-angiotensin system in the kidney. When intravascular volume falls, the renin-angiotensin system is stimulated, and aldosterone is released from the adrenal gland, resulting in increased reabsorption of sodium in exchange for increased excretion of potassium and hydrogen. The increased sodium reabsorption will cause more water to also be reabsorbed by the kidney. If too much circulating volume is sensed by the atria, natriuretic peptides are released, resulting in a diuresis. Angiotensin II also stimulates the thirst centres.

Sodium

Sodium is the most prevalent cation in the extracellular fluid. This is maintained by Na⁺/K⁺ pumps across the cell membrane. The total body sodium is therefore proportional to ECF volume. Sodium homeostasis is primarily restricted to the extracellular space. Despite great variation in the intake of both sodium and water, close control of serum sodium is maintained via control of the excretion of water and sodium by the kidney and thirst. Over 99% of the sodium filtered by the kidney is reabsorbed in the proximal tubule and loop of Henle. This reabsorption occurs at a relatively fixed rate, regardless of total body sodium. It is the smaller proportion of sodium, reabsorbed in the distal tubule and collecting ducts that exert the most influence on total sodium balance. This is regulated by the renin-angiotensin-aldosterone system. Thirst is stimulated by an increase of a few percent in plasma [Na⁺] and a decrease in the effective circulating volume [part of the extracellular volume (ECV) that effectively perfuses the tissue]. Changes in Na⁺ will result in alteration in osmolality and thus fluid movement between the ECF and the ICF. Recent experimental work suggests that sodium may be stored in tissues such as skin and muscle and may be regulated by macrophages. The concept of extrarenal regulation of sodium homeostasis provides new avenues for the preclinical and clinical research

Hyponatraemia

As sodium and its accompanying anions are the major effective plasma solutes in the ECF, it is common to for low sodium to level to exist with low, normal or high osmolality see figure 1 Further it may be useful to classify hyponatraemia based on fluid status. Traditional classifications according to volume status are notoriously difficult to handle in clinical practice. Following a simple algorithm for the diagnosis and treatment of hyponatraemia has been shown to be associated with improved outcomes. See figure 1. Measure sodium and plasma osmolality, assess volume status and determine spot urine sodium and osmolality.

Hypo-osmolar hyponatremia

“True hyponatremia” is regarded as a low sodium level in the presence of hypoosmolality. This is because sodium in the ECF and potassium in the ICF (along with their associated anions) determine osmolality, with water moving freely between fluid compartments, to maintain the same osmolality between compartments. As a result, plasma hypo-osmolality, indicates a relative excess of water to sodium, regardless of volume status. It is an oversimplification to regard hypo-osmolar states as a product of either water excess or solute depletion, as often both are involved.
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Hypertonic hyponatraemia

Hypotonic hyponatraemia

Hypovolaemic hyponatraemia

Euvolaemic hyponatraemia

Hypervolaemic hyponatraemia

Pseudohyponatraemia

Normo-osmolar hyponatraemia

Figure 1  
Hyponatraemia

**Hypo-osmolar hypovolaemic hyponatraemia**

The total body water and total body sodium are both low, but there is disproportionate loss of sodium compared with water. This is a result of the increased ADH secretion seen in hypovolaemic states causing increased water reabsorption. Hyponatremia is often compounded by thirsty patients consuming hypotonic fluids at a level inadequate to try to restore circulating volume. Sodium loss can be renal or extra-renal. A urinary sodium level below 20 mmol/l is suggestive of an extra-renal cause. Extra renal causes may be due to gastrointestinal loss (common), exercise (also commonly seen in people working in hot conditions), burns, trauma, and pancreatitis. A urinary sodium concentration greater than 20 is due to renal causes, diuretic excess, renal failure, salt wasting nephropathy, aldosterone deficiency, chronic pyelonephritis, nephrocalcinosis, proximal renal tubular acidosis and ketonuria.

**Hypo-osmolar euvolaemic hyponatraemia**

The syndrome of inappropriate ADH (SIADH) is the most common cause of euvolaemic hyponatremia and has numerous causes. If SIADH is suspected, it can be useful to measure urine osmolality. A urine osmolality >100 mOsm/kg in the presence of hyponatraemia reflects inappropriate antidiuresis. Other causes include glucocorticoid insufficiency hypothyroidism and drugs e.g. SSRIs

**Hypo-osmolar hypervolaemic hyponatraemia**

This is a situation characterised by a paradoxical increase in total body sodium, but a simultaneous and proportionally larger increase in total body water leading to a dilutional hyponatremia. This reduction in water excretion is secondary to either an excess of AVP secretion or renal impairment limiting the maximal excretion of free water. The increase release of AVP may be due a decrease in arterial effective volume this is seen in nephrotic syndrome, congestive cardiac failure (CCF) and cirrhosis. Such patients commonly have a raised spot urine sodium and osmolality. In renal failure patients are unable to reabsorb sodium and have water retention due decrease filtration. They will often have an increase in urine sodium and often decrease urine osmolality.

**Normo-osmolar hyponatraemia**

Hyponatraemia occurring without hypo-osmolality is referred to as pseudohyponatraemia. Pseudohyponatraemia can occur with a normal or elevated serum osmolality. Pseudohyponatraemia with normal serum osmolality occurs when grossly elevated levels of lipids or proteins lead to an artificial apparent decrease in measured serum sodium. This is because sodium normally distributes in the aqueous phase of plasma which accounts for 93% of the plasma volume. A correction factor for whole plasma can be rendered incorrect if the non-aqueous phase is increased due to hypertriglyceridaemia or paraproteinaemia. The use in laboratories of direct ion-sensitive electrodes
instead of a flame photometer eliminates this potential error. Glycine often used in urological procedures and mannitol are unable to cross the cell membrane and remains in the plasma resulting in movement of water from the intracellular space into the ECF thus causing a decrease in sodium concentration and an increase in the effective osmolality. Glucose normally diffuses freely into cells but when insulin is deficient, glucose is effectively confined to the ECF. When the concentration of glucose rises, water moves across the membrane from inside to outside the cell, dehydrating the cell, and causing a dilutional hyponatraemia. In diabetic ketoacidosis, the “true” corrected serum sodium can be estimated from the formula: \([\text{Na}^+]_{\text{corrected}} = [\text{Na}^+]_{\text{measured}} + ((\text{glucose}-5.6) \times 0.288)\). or \([\text{Na}^+]\) is reduced approximately 0.4 mmol/l per mmol/l increase in P-[Glc] eg. If the patient’s measured glucose is 20mmol/l and the measured Na⁺ is 122 mmol/l then the true Na⁺ is approximately 127 mmol/l

Hyper-osmolar hyponatraemia

An increase in sugars eg glucose mannitol and sorbitol and radio contrast media cause an increase in osmolality and cause an increase in fluid influx into the ECF from the ICF resulting in a decrease in Sodium concentration.

Hypernatraemia

Hypernatraemia is caused by net water loss (increased loss or decreased intake) or, rarely, sodium gain. Patients at increased risk include those with an impaired thirst mechanism or restricted access to water (e.g., those with altered mental status, intubated patients, infants, older adults). See figure 2

Figure 2

Hypernatraemia

Treatment

Both Hyponatremia and hypernatraemia cause significant morbidity and mortality. Both require urgent management. Too rapid correction may result in significant brain injury. Whether treating hyponatremia or hypernatraemia, the concentration of sodium should not change by more than 8 – 10mmol/l per 24hours.

References

Available on request

Suggested article.

Braun M M, Barstow C H, Pyzocha N J. Diagnosis and Management of Sodium Disorders: Hyponatremia and Hypernatremia Am Fam Physician. 2015;91(5):299-307