This article describes the factors that influence water and sodium homeostasis, as well as the associated clinical problems encountered when having to assess and manage a patient with these imbalances.

NORMAL WATER AND ELECTROLYTE DISTRIBUTION

Approximately two-thirds of the total body water is found in the intracellular fluid ‘compartment’ (ICFC), and one-third in the extracellular fluid ‘compartment’ (ECFC). The ECFC consists of the intravascular (1/4 ECFC) and interstitial spaces (3/4 ECFC) (Fig. 1).

The total water content of the body differs according to age and gender – this is significant when replacing fluid in dehydrated patients (Fig. 2).

A 70 kg young male would have an estimated total body water content of 42 l, ICFC ≈ 23 l, ECFC ≈ 19 l (interstitial fluid ≈ 16 l and intravascular fluid ≈ 3 l).

Na⁺ is the major cation of the ECFC and K⁺ is the major cation of the ICFC (Fig. 1). The tendency for these cations to move down their individual concentration gradients is opposed by the Na⁺:K⁺ ATPase pump which constantly extrudes Na⁺ out of cells (in exchange for K⁺). Under normal circumstances, the ECF [Na⁺] is the main contributor of the ECFC tonicity.

Mg²⁺ and PO₄³⁻ ions are found predominantly intracellularly, while Cl anions are found predominantly in the ECFC in association with Na⁺ ions.

Water, on the other hand, is freely permeable across the membranes of the ICFC and ECFC and water distribution is determined by the (osmotically active) particular content of the various compartments. At the capillary level, the oncotic pressure (osmolality due to the protein content) of plasma determines the fluid content of the interstitial space. Osmolality differences between compartments are corrected by fluid shifts.
70 kg male.

Fig. 3. Input-output chart of a healthy and free-water clearance is impaired.

Normal cortisol levels are required for the renal clearance of the body’s normal solute load. A normal person requires 500 ml of water in exchange for H+ and K+.

Loss of ISO TONIC fluid – small intestinal secretions e.g. fistulae, paralytic ileus, small bowel obstruction, new ileostomies

Loss of HYPOTONIC fluid – vomitus

Loss of HYPERTONIC fluid – diarrhoeal fluid

Loss of ‘pure’ water – sweat, as in pyrexial patients

Other factors that stimulate ADH secretion are stress, nausea and drugs, e.g. morphine, barbiturates, chlorpropamide, carbamazepine. Examples of drugs that suppress ADH secretion are alcohol, phenytoin and atropine.

The effect of fluid loss on the body depends on what type of fluid is lost (Fig. 4), the rapidity of the loss and the attempt at replacement (if any).

SODIUM HOMEOSTASIS

The average oral intake is 100 - 200 mmol sodium/day. Major daily losses are via the kidney, although only < 1% of the 25 000 mmol Na+ that is filtered daily by renal glomeruli appears in the urine (fractional excretion of Na+).

Factors that regulate renal sodium include the glomerular filtration rate (GFR), the renin-angiotensin-aldosterone system (RAAS) and natriuretic peptide secretion. As the GFR decreases, Na+ reabsorption increases and the opposite is true for an increase in GFR.

A decrease in renal blood flow (as in dehydration) causes renin secretion by the cells of the juxtaglomerular apparatus in the kidney. Renin converts angiotensigen to angiotensin I, which in turn is converted to angiotensin II by the action of angiotensin-converting enzyme (ACE). Angiotensin II has a direct vasoconstrictor action, as well as stimulating the secretion of aldosterone from the adrenal cortex (secondary hyperaldosteronism). Aldosterone acts on the distal renal tubules and Na+ is reabsorbed in exchange for H+ and K+.

Natriuretic peptides – atrial natriuretic peptide (ANP), brain-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP) – are secreted in response to an increase in the intravascular volume and serve to protect against fluid overload. Cardiac atrial stretch causes release of ANP and BNP, which result in natriuresis, diuresis, kaliuresis and a reduction in blood pressure.

HYPONATRAEMIA

Consequences of ECF hypo-tonia

When hypotonic hyponatraemia develops acutely, water moves from the ECFC into the ICFC along the osmotic gradient, causing swelling of cells within minutes. This response is particularly undesirable in the brain, as cerebral oedema could progress to brain-stem herniation, respiratory arrest and possibly death.

There is, however, a rapid adaptation, resulting in loss of intracellular solutes, especially K+, causing the cells to decreases in size towards normal. However, if the rate of water loading is faster than this rate of adaptation then the patient will be symptomatic. Symptoms include lethargy, seizures, confusion, coma, respiratory arrest and even death.

If, on the other hand, the change in the ECF hypotonicity occurs slowly, then the cells, in particular the brain cells, are able to adapt more effectively as the tonicity changes.
For this reason, in patients with the same low [Na\(^+\)], chronic hyponatraemia is better tolerated than acute hyponatraemia and lethargy and restlessness may be the only symptoms. When the serum [Na\(^+\)] is < 110 mmol/l, and the patient is symptomatic, care has to be taken not to correct the hyponatraemia too rapidly. In the adapted state, the initially swollen cells have been reduced to normal volume by loss of solute. With a rapid increase of the ECF osmolality (by the therapeutic infusion of hypertonic solutions), fluid will move out of the cells, and the ensuing rapid cell shrinkage will result in osmotic demyelination of pontine and extrapontine neurones (myelinolysis) with permanent neurological damage, coma and even death. Rapid correction may be better tolerated in acute hyponatraemia.

Approach to hyponatraemia

Iso-osmolar hyponatraemia (factitious)

In the approach to hyponatraemia, pseudohyponatraemia should be excluded first. This term refers to a low plasma Na\(^+\) measurement when the measured osmolality is normal.

An aliquot of normal plasma contains about 7% solids, which include proteins and lipids. The remaining 93% of plasma consists of water (containing dissolved Na\(^+\) ions).

In conditions like multiple myeloma and hyperlipidaemia, where the solid fraction of the plasma sample in the collection tube is markedly reduced, due to displacement of water molecules by the excessive paraproteins or lipids respectively. This reduced water phase will thus have fewer dissolved Na\(^+\) molecules. The [Na\(^+\)] is expressed in terms of the total volume of plasma sampled and the factitious low reading represents an exaggerated negative analytical error.

Hyperosmolar hyponatraemia

Hyponatraemia in a patient with a high measured osmolality indicates the presence of increased amounts of other osmotically active solutes apart from Na\(^+\) in the ECF. This ECF hyperosmolality causes water shift from the ICFC, diluting out the ECF Na\(^+\).

The causes of hyperosmolar hyponatraemia include hyperglycaemia and the use of mannitol.

Hypo-osmolar hyponatraemia (true hyponatraemia)

Both the measured plasma osmolality and [Na\(^+\)] are low. Because the plasma [Na\(^+\)] is an index of the water balance, the cause of the hyponatraemia is determined by assessing ECF volume. This is accomplished by taking the patient history, measuring the body mass and assessing the state of hydration and jugular venous pressure (JVP) on physical examination. There may be:

- **Hypovolaemia** – loss of water and Na\(^+\) with attempted replacement using sodium-deficient fluid, e.g. tap water, 5% IV glucose.
- **Renal losses** – osmotic diuresis, diuretics, aldosterone deficiency, or salt-losing nephritis.
- **Extrarenal losses** – excessive sweating, vomiting, or diarrhoea.

Slight hypertovolaemia with no oedema. If there is ‘pure water’ gain (normal total body Na\(^+\)) then there will be no oedema because the excess water will redistribute itself across both the ECFC and ICFC. Increased water intake can be the result of inappropriate salt-free IV fluids or psychogenic polydipsia (compulsive drinking of excessive quantities of water). Decreased water excretion can be caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH), cortisol deficiency, severe hypothyroidism, or drugs, e.g. oxytocin.
• Hypervolaemia with oedema.
  In conditions where there is retention of both Na⁺ and water (increased total body water and Na⁺), e.g. nephrotic syndrome, cardiac failure, cirrhosis, water may be retained in the interstitial space (oedema) at the expense of the intravascular compartment. Oedematous states are often refractory to diuretic therapy and are found in hypoalbuminaemic conditions. Plasma expanders like albumin may have to be administered.

SICK CELL SYNDROME

Hyponatraemia is not infrequently seen in acute or chronically ill patients. The term ‘sick cell syndrome’ is used in those patients where no obvious cause for the hyponatraemia can be found.

The exact mechanism of the hyponatraemia has not yet been determined, although it is believed to be due to increased membrane permeability (redistribution hyponatraemia). A contributory factor may be the increase in ADH secretion that occurs in ill patients due to stress. Treatment of the underlying illness eliminates the hyponatraemia.

SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

In this syndrome, despite the hypo-osmolar hyponatraemia, ADH continues to be secreted inappropriately, resulting in a dilutional hyponatraemia.

Essential diagnostic criteria for SIADH:
• Hypo-osmolar hyponatraemia.
• The urine osmolality is high relative to the serum sample collected at the same time.
• The spot urine [Na⁺] is high (> 20 mmol/l). This is because the slight hypervolaemia due to water retention does not stimulate the RAAS and, in addition, stimulates the release of ANPs, which cause natriuresis.
• The patient should have no evidence of hypovolaemia or oedema.

• Disorders of the heart, pituitary, adrenals, kidneys and thyroid have to be excluded as they can produce similar biochemical features.
• The patient should not be on drugs that stimulate ADH secretion (e.g. morphine), potentiate ADH effect (e.g. indomethacin), or produce similar biochemical features (e.g. thiazide diuretics).
• The hyponatraemia should respond to water restriction.
• If the above criteria are met, then an increased ADH can be assumed.

Consequences of hypernatraemia
The resultant hypertonic ECF causes water to move from the ICFC into the ECFC down the osmotic gradient, thereby shrinking cells. Partial cellular recovery occurs within minutes due to solute movement (mainly Na⁺ and Cl⁻) into cells. Many cell types, particularly brain cells, have an additional slower adaptive mechanism. They are able to produce osmotically active products of cellular metabolism, known as idiogenic osmoles, which include taurine, glycine, glutamine, sorbitol and inositol.

As in hyponatraemia, rapid correction of hypernatraemia, in this case with hypertonic fluids, can be dangerous, especially at the stage where cells have undergone slow osmotic adaptation. Rapid correction will result in swollen brain cells; the patient may have seizures and become comatose. The water deficit should therefore be corrected slowly over 48 - 72 hours.

Approach to hypernatraemic states (Fig. 6)

With euvolemia
When there is a loss of pure water from the body, this loss is shared across both ECFC and ICFC (Fig. 7). Circulatory failure is therefore only a late feature in these cases and only when the [Na⁺] is >160 - 170 mmol/l. Replacement should be with tap water.

An example is diabetes insipidus (DI), which can be cranial or nephrogenic. In cranial [central] DI, ADH is deficient due to pituitary or hypothalamic disease, while in nephrogenic DI, despite normal ADH secretion, the kidneys are unable to respond (ADH resistance) due to either inherited or acquired causes. Both types present with polyuria and polydipsia and a fluid deprivation test has to be performed to distinguish between them.

With hypovolaemia
These patients develop hypernatraemia because of loss of hypertonic fluids. In this instance, although the total
body Na⁺ is depleted, the net loss of water from the ECFC is greater. Hypernatraemia is particularly evident when there is failure to respond to thirst, as in the unconscious patient who has had no replacement of the losses, or the patient who has an impaired thirst centre, e.g. the elderly, or patients with head injuries.

If hypotonic fluid is considered as having isotonic and pure water components, the loss of hypotonic fluid will be seen to result in proportionally more ECFC volume depletion than would an equivalent amount of pure water. As the ECF volume decreases, there may be signs of shock and if left uncorrected, it may result in the complication of acute tubular necrosis.

To prevent this, the ECFC should be rapidly expanded with isotonic fluid (normal saline) until the blood pressure and renal function are restored, and thereafter the pure water deficit can be corrected more slowly. Examples include renal loss due to osmotic diuresis and extrarenal loss due to vomiting, diarrhoea and sweating.

**Hypervolaemia**

There is a gain in both water and Na⁺, although in this instance, the net gain of Na⁺ is relatively more (increased total body water and Na⁺), e.g. mineralocorticoid excess as in Conn’s syndrome. Patients characteristically do not have oedema and present with hypertension. The underlying cause must be treated.

**CONCLUSION**

Sodium homeostasis is intimately linked with water balance within the body. It is important to consider whether ‘pure’ fluid losses or gains occurred in isolation or whether they occurred concurrently with salt loss or gain. The duration of the loss also has significant consequences. The patient’s physical presentation together with presence of either hyper/hyponatraemia, influence the type of replacement fluid selected, as well as the replacement rate. Injudicious saline-poor or saline-rich fluid administration can result in increased morbidity and mortality.

**Further reading**


**IN A NUTSHELL**

ECF [Na⁺] is the main contributor of the ECFC tonicity. When there is pure water loss from the ECFC due to diabetes insipidus, this loss is shared across both intracellular and extracellular compartments. Dehydration is therefore only a late sign.

When there is loss of both water and sodium from the ECFC, as in diarrhoea and vomiting, this loss is borne mainly by the ECFC. Dehydration is therefore an early sign.

Hypernatraemia is always associated with an increase in the measured plasma osmolality. Hyponatraemia can be associated with a normal, increased or decreased measured plasma osmolality.

Rapid correction of hyponatraemia or hypernatraemia after cellular adaptation has taken place can lead to irreversible demyelination of pontine and extrapontine neurones (myelinolysis).

SIADH is only diagnosed after excluding cardiac, pituitary, adrenal, thyroid and renal disorders as well as the effect of drugs.

Biochemical features of SIADH are true hyponatraemia, an inappropriately concentrated urine and a urine [Na⁺] > 20 mmol/l (plasma and urine samples collected at the same time).