WATER AND SODIUM DISTURBANCES

A large proportion of the body consists of water. Sodium is the major electrolyte that influences the water content and its distribution.

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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).

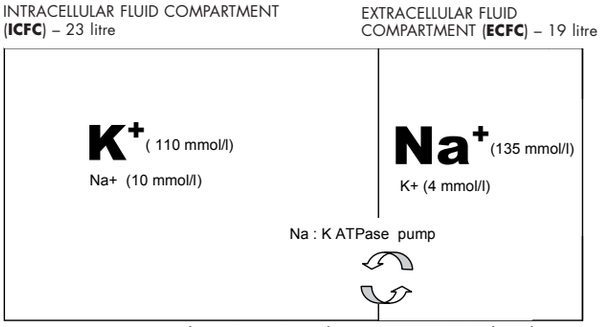

Fig. 1. Water, sodium (Na^+) and potassium (K^+) distribution in the different body compartments of a young 70 kg male (total body water is 42 l).

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).

Infants	–	75% TBW
Young males	–	60% TBW
Young females	–	55% TBW
Elderly males	–	50% TBW
Elderly females	–	45% TBW

Fig. 2. Water distribution according to age and gender expressed as a % of total body weight (TBW).

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.

Mg^{2+} and PO_4^{3-} 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.

WATER BALANCE

A well-balanced fluid state depends upon fluid input, output and fluid shifts. A 70 kg young adult male might have an average daily balance as seen in Fig. 3.

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OUPUT		INPUT	
Skin	500 ml	Metabolism	400 ml
Lungs	400 ml	Diet	1 100 ml
Gut	100 ml		
Kidney	1 500 ml		
	2 500 ml		2 500 ml

Fig. 3. Input-output chart of a healthy 70 kg male.

This balance can vary greatly depending on the availability of water, environmental factors (heat, humidity), physical activity, fluid losses during illness (e.g. diarrhoea/vomiting/polyuria/sweating due to pyrexia/respiratory loss due to tachypnoea), glomerular filtration, renal tubular concentration and dilution ability, as well the manner in which fluid is replaced.

Free water clearance by the kidney (or urine dilution) is the hypothetical rate at which water is excreted in excess of that required for the renal clearance of the body's normal solute load. A normal person requires 500 ml of tubular fluid to eliminate approximately 600 mmol of solute daily.

An increase in plasma osmolality or a decrease in blood volume stimulates the thirst centre in the hypothalamus.

Both an increase in plasma osmolality of > 2% and a decrease in intravascular volume of > 10% stimulate the release of antidiuretic hormone (ADH) (also known as arginine vasopressin) from the posterior pituitary. ADH binds to the V2 receptors on the basolateral membrane of the renal collecting tubules. This induces the insertion of water channels called aquaporins into the luminal surface.

Water is passively reabsorbed via these aquaporins down a concentration gradient created by the hyperosmolal renal medulla. Urine is thus concentrated and there is decreased free-water clearance.

Normal cortisol levels are required to inhibit ADH release. In cortisol-deficient states, e.g. Addison's disease, ADH continues to be secreted and free-water clearance is impaired.

Loss of ISOTONIC fluid	–	blood
	–	small intestinal secretions e.g. fistulae, paralytic ileus, small bowel obstruction, new ileostomies
Loss of HYPOTONIC fluid	–	vomitus
	–	diarrhoeal fluid
	–	sweat, as in pyrexial patients
Loss of HYPERTONIC fluid	–	loss of hypotonic body secretions replacement with tap water has the net effect of loss of 'hypertonic' fluid
Loss of 'pure' water	–	loss of dilute urine in diabetes insipidus

Fig. 4. Types of fluid loss.

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 angiotensinogen 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 hypotonia

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 decrease 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.

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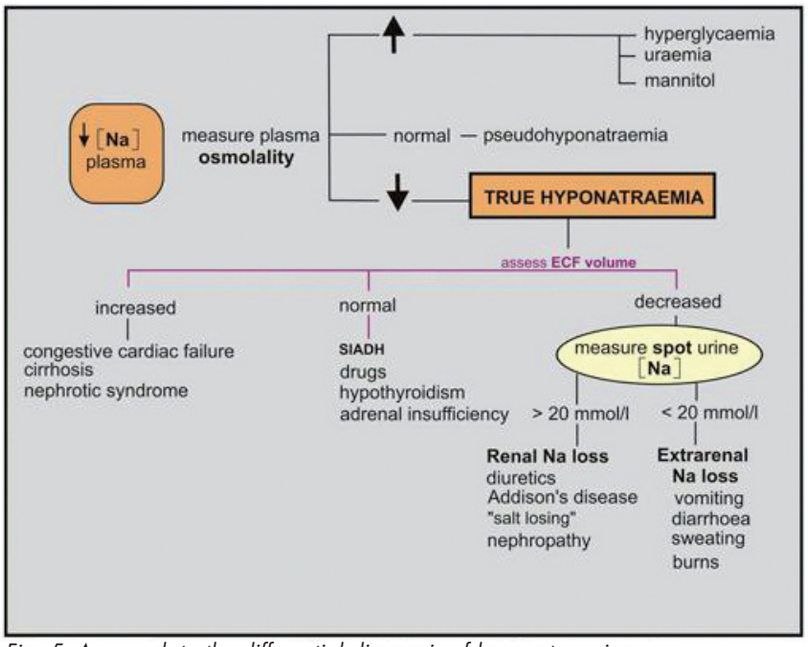

Fig. 5. Approach to the differential diagnosis of hyponatraemia.

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 (Fig. 5)

Iso-osmolal 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 is increased, the water content 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.

Hyperosmolal 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 ECFC. This ECFC hyperosmolality causes water shift from the ICFC, diluting out the ECF Na^+.

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

Hypo-osmolal 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 hypervolaemia 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.

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- **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-osmolal 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.

Causes of SIADH:

- Malignancies – e.g. carcinoma of the bronchus, brain, kidney and intestine; lymphomas.
- Cerebral disorders – infections, trauma, tumours.
- Pulmonary disorders – pneumonia, tuberculosis, pneumothorax.
- Other – Guillain Barré syndrome, acute intermittent porphyria.

Management of water overloading

- **Acute water overload**. This is a medical emergency due to a rapidly expanded brain volume. The aim of therapy is to prevent progression, as well as to reverse this process. When the serum [Na^+] is < 110 mmol/l and the patient is symptomatic, hypertonic saline (5% NaCl) is infused until the [Na^+] is 120 mmol/l. Excessive expansion of the ECFC and the subsequent development of pulmonary oedema and cardiac failure can be prevented with the concurrent administration of furosemide. Oral fluids should be restricted.

- **Chronic water overload**. Chronic water overload may be seen in SIADH. If the patient is symptomatic the treatment will be as for acute water overload. Oral fluid restriction may suffice in the asymptomatic patient. Aggressive rapid correction can be fatal.

HYPERNATRAEMIA

Unlike hyponatraemia, hypernatraemia is always associated with an increase in the measured plasma osmolality.

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 hypotonic 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 euvolaemia

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 hypotonic fluids. In this instance, although the total

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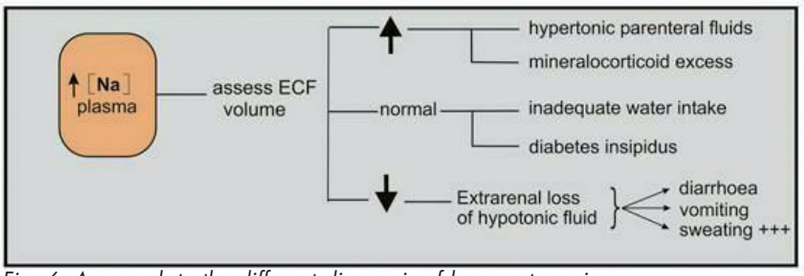

Fig. 6. Approach to the different diagnosis of hypernatraemia.

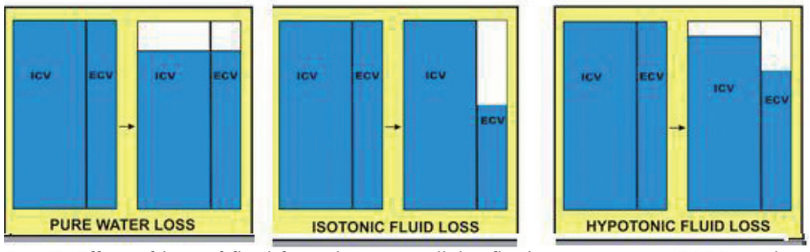

Fig. 7. Effect of loss of fluid from the extracellular fluid compartment (ECFC) without replacement with oral/intravenous fluid.

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

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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).

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