Sodium

1 Name and description of analyte

1.1 Name of analyte
Sodium (serum, plasma, whole blood and urine)

1.2 Alternative names: none
Chemical symbol: Na (from the Latin, Natrium)

1.3 NLMC code: to follow

1.4. Function(s) of analyte

1. Sodium is the main cation in the extracellular fluid (ECF) and is the principal contributor to the osmolality of the ECF.
2. Sodium is closely linked to water homoeostasis; changes in extracellular water volume will cause a change in [sodium].
3. Movement of sodium plays an important role in maintaining the electrical potential across cell membranes that is essential for muscle and neural cell activity. The Na^+,K^+-ATPase actively transports sodium out of cells in exchange for potassium, to maintain the electrochemical gradient between the intra- and extracellular compartments.

Sodium intake is via the diet and excretion is predominantly through the kidneys. There is also a small obligatory loss of sodium from the gastrointestinal tract and skin. In the kidneys, the bulk of filtered sodium undergoes obligatory reabsorption in the proximal convoluted tubules and loops of Henle. Sodium excretion is regulated by the action of the renin–angiotensin–aldosterone system. Aldosterone stimulates sodium reabsorption (in exchange for potassium and hydrogen ions) by the distal renal tubules (and also the distal colon, and sweat and salivary glands).

Anti-diuretic hormone (ADH, vasopressin), which is released from the posterior pituitary, causes water reabsorption primarily in the collecting ducts. It is secreted in response to increased plasma osmolality and reduced intravascular volume. Osmolality is the more important physiologic effector, but a severe decrease in intravascular volume can over-ride this and increase ADH secretion. Increased plasma osmolality also stimulates thirst and hence water intake. Atrial natriuretic peptide (ANP) secreted from the right atrium and brain natriuretic peptide (BNP) secreted from the ventricles. Both are released in response to increased blood volume and also plasma osmolality. ANP and BNP act mainly on the kidneys to stimulate sodium excretion and antagonise the action of the renin–angiotensin–aldosterone system.

2 Sample requirements and precautions

2.1 Medium in which measured
1. Sodium can be measured in serum, plasma (lithium heparin) or heparin-anticoagulated whole blood (the last of these only by the use of a direct ion selective electrode).

2. Sodium can be measured in urine, either in random ('spot') specimens or 24 hour collections. No preservative is required.
3. Sodium can also be measured in interstitial fluid and sweat, but such measurements are not considered in this article.

2.2 Precautions re sampling, handling etc.

- Contamination of sample with IV infusions: samples must not be taken from an arm into which an IV infusion is running.
- Contamination from blood tubes containing sodium citrate.
- Severe haemolysis can cause a dilutional effect, leading to a falsely lowered [sodium].

3 Summary of clinical uses and limitations of measurements

3.1.1 Uses (serum, plasma)

1. Monitoring patients with dehydration or excessive fluid losses.
2. Monitoring patients with oedema.
3. Monitoring patients on parenteral fluid replacement.
4. Monitoring the treatment of patients with hyperglycaemic conditions (ketoacidosis and hyperosmolar hyperglycaemic state).
5. Monitoring patients on drugs known to cause hyponatraemia or (less often) hypernaatraemia.
6. Investigation of patients with unexplained central neurological symptoms or signs.
7. Calculation of the osmolar gap.
8. Calculation of the anion gap in acid-base disturbance.

3.1.2 Uses (urine)

1. Investigation of hyponatraemia.
2. Investigation of oliguria.
3. Assessment of dietary sodium intake.

3.1.3 Limitations

Sodium and water homoeostasis are closely linked, so plasma [sodium] alone provides neither information about the sodium content of the extracellular fluid nor of total body sodium content.

4 Analytical considerations

4.1 Analytical methods

Sodium can be measured by a variety of techniques including direct and indirect ion-selective electrodes (ISE), flame photometry, atomic absorption spectrophotometry and dry slide techniques. Most laboratories and point-of-care testing devices use ISE methods.

ISEs for sodium use specific membranes, often a glass membrane or liquid ion-exchange membrane (in which a neutral ion-specific carrier substance is dissolved in an inert solvent). The membrane is in contact with the test solution and an internal reference solution of known concentration. Due to the specific nature of the membrane the sodium ions closely associate with the membrane. The interaction of the ions with the membrane

causes a change in electromotive force. This measuring electrode is connected to a reference electrode (containing solutions of known concentration) via a high resistance voltmeter. The difference in electrical potential between the two electrodes is measured. The Nernst equation is then used to determine the concentration of sodium in the test solution. In indirect ISE methods the test sample is diluted before measurement and assumptions are made regarding the aqueous proportion of a unit volume. Most laboratory methods use indirect ISE methods. In direct ISE methods the sample is presented to the electrode without dilution; this is common in point-of-care methods (such as blood-gas analysers) that use whole blood samples. Direct ISEs measure *activity* in the aqueous component of plasma rather than *concentration* in a unit volume of blood.

4.2 Reference method
Flame emission spectrophotometry.

4.3 Reference materials
Sodium chloride (Standard Reference Material 919b, National Institute of Standards and Technology, USA).

4.4 Interfering substances
1. Indirect ISE methods (and flame emission spectrophotometry) can give errors owing to the electrolyte exclusion effect. Severe hyperproteinaemia and hyperlipidaemia causes pseudohyponatraemia, due the reduction in the volume of plasma that is water. This problem is not encountered in sodium measurement by direct ISE.

4.5 Sources of error
Sources of error with ISEs:

- lack of selectivity
- protein coating on ion-selective membrane
- contamination of the membrane by competing ions eg. potassium, ammoninum and lithium

5 Reference intervals and variance

5.1.1 Reference interval (adults)
Plasma and serum: 133-146 mmol/L.
Urine: variable, depending on sodium intake and clinical state. In health, urinary excretion should equal intake less losses from other sources e.g. the gut. Sodium excretion on an average diet is 40-220 mmol/24 h; 'spot' urine [sodium] can fall to zero (<10 mmol/L) in sodium depletion, if renal function is normal.

5.1.2 Reference intervals (others)
Paediatric reference range is the same as for adults.
Hospitalised patients tend to have lower sodium concentrations (by ~ 1-3 mmol/L) than those in the community.

5.1.3 Extent of variation

5.1.3.1 Interindividual CV 1.6%

5.1.3.2 Intraindividual CV 1.3%
5.1.3.3 Index of individuality: 0.81
5.1.3.4 CV of method: 0.7%
5.1.3.5 Critical difference: 4%

5.1.4 Sources of variation

Urine: sodium excretion is determined by dietary intake; also, sodium has a diurnal excretion with peak excretion occurring during the day.

6 Clinical uses of measurement and interpretation of results

6.1.1 Indications for measurements and interpretation of results (plasma, serum, blood)

1. Monitoring patients with dehydration or excessive fluid losses. Patients who are at risk of dehydration because of excessive fluid losses should have their serum sodium measured as part of the monitoring of fluid volume status. A raised serum [sodium], usually indicates loss of water and can be used in conjunction with other parameters such as urea and, creatinine and with clinical assessment to determine whether there is extracellular fluid depletion. Hyponatraemia may be found in patients who are losing sodium and water, such as those with diarrhoea or high output stomas.

2. Monitoring patients with oedema. Patients with oedema usually have an excess of sodium and water, with water retention in excess of sodium, leading to hyponatraemia. Some common causes of this are heart failure, liver disease and nephrotic syndrome.

3. Monitoring of patients on parenteral fluid replacement. Patients who are receiving parenteral fluid or nutrition should have their serum sodium measured (to be used in conjunction with fluid balance charts, measurement of other electrolytes and clinical examination) to ensure that the patient is euvolaemic. Close attention should be paid to monitoring the serum sodium of patients who have high sodium losses.

4. Monitoring of patients with hyperglyaemic conditions. Patients with hyperglycaemia have an osmotic diuresis and a tendency to hypernatraemia due to net loss of water. However, in diabetic ketoacidosis, other factors may counterbalance this and hyponatraemia may occur. Treatment with insulin stimulates cellular glucose uptake and the associated osmotic drag of water raises extracellular [sodium].

5. Monitoring patients on drugs known to cause hyponatraemia or hypernatraemia (see section 7).

6. Patients with unexplained central neurological symptoms or signs should have their serum [sodium] measured. Changes in serum [sodium] cause osmotic shifts that can cause disruption of nervous system cells owing to swelling and shrinkage. Acute changes in serum [sodium] tend to cause greater damage and hence more severe symptoms or signs.

7. Calculation of osmolarity and osmolal gap. Osmolarity can be calculated by a formula that sums the molar concentrations of the solutes that normally contribute most to the osmolality of serum. There are several variations of the formula, one of which is:

$1.89[Na^+] + 1.38[K^+] + 1.03[\text{urea}] + 1.08[\text{glucose}] + 7.45$

The osmolal gap is the measured osmolality minus the calculated osmolarity. A value >10 mmol/L suggests the presence of another osmotically active substance(s) e.g. ethanol, methanol, ethylene glycol.

7. Calculation of the anion gap in acid-base disturbance. Serum anion gap is calculated as: ($[Na^+]$ + $[K^+]$) − ($[Cl^-]$ + $[HCO_3^-]$). The normal anion gap is 10-18 mmol/L. A high anion gap can help identify the cause of a metabolic acidosis.

6.1.2 Indications for measurement and interpretation of results (urine)

1. Investigation of patients with hyponatraemia. In conjunction with clinical assessment of extracellular fluid volume status and urine osmolality, random urine [sodium] may be used as an indirect index of aldosterone activity. Urine sodium <20 mmol/L implies ECF volume depletion, while a value of >30 mmol/L is seen with a normal or increased volume.
2. Investigation of patients with oliguria. Random urine sodium <20 mmol/L indicates both appropriate secretion of aldosterone and renal response. Random urine sodium >30 mmol/L implies either insufficient aldosterone secretion or inability of the kidneys to respond to the hormone, as occurs in adrenal insufficiency and acute kidney injury.
3. Assessment of sodium intake. In a steady state, urinary sodium excretion reflects dietary intake (less other losses, e.g. in sweat).

6.2 Confounding factors

None.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

Most commonly due to water loss, also combined sodium and water loss with water loss predominating; rarely to sodium excess.

1. Water loss
    - Inadequate water intake
    - impaired mental state
    - restricted access to water
    - diminished thirst response (eg. in the elderly or as a result of hypothalamic lesions)
- Renal loss
    - diabetes insipidus (cranial and nephrogenic)
- Increased insensible losses
    - fever
    - mechanical ventilation.

2. Water and sodium loss
- Skin
    - excessive sweating (e.g. in endurance sports)
    - burns
- Gastrointestinal
    - diarrhoea
    - vomiting
    - fistulas
    - nasogastric tube drainage
- Renal

- osmotic diuresis (e.g. diabetes mellitus)
- diuretic drugs
- diuretic phase of acute kidney injury.

3. Sodium excess

- Iatrogenic
  - sodium bicarbonate
  - hypertonic saline infusion
  - intravenous antibiotics containing sodium
  - hypertonic dialysis
  - tube feeding
  - use of saline to replace pure water loss
- Hyperaldosteronism
- Excess sodium ingestion
  - inadvertent
  - deliberate poisoning
  - ingestion of sea water.

7.1.2 Investigation

- History and clinical examination should reveal the cause of hypernatraemia in most cases.
- Current or previous history of lithium use is highly likely to indicate diabetes insipidus (nephrogenic)
- In hypernatraemia the plasma osmolality is always raised.
- In hypernatraemia urine osmolality is usually raised (often to >750 mmol/kg); however, in diabetes insipidus, large volumes of dilute urine are produced and the urine osmolality is in appropriately low (less than this and sometimes <100 mmol/kg).
- Measure plasma glucose to exclude osmotic diuresis secondary to raised blood glucose.
- Plasma [urea] and [creatinine] may be increased as a result of water loss or sodium and water loss.

7.2 Low values

7.2.1 Causes

The main mechanisms causing hyponatraemia are depletion of sodium or increase of water in the extracellular fluid, or excess of both water and sodium in the interstitial space.

1. Loss of sodium

- Renal
  - diuretics
  - renal tubular acidosis
  - mineralocorticoid deficiency
  - cerebral salt wasting
- Gastro-intestinal tract
  - diarrhoea
  - vomiting
  - enterocutatneous fistula
  - intestinal obstruction
- Skin

- burns
- excess sweating
- cystic fibrosis
- extensive dermatitis.

2. Water excess

- Increased water intake
  - excessive IV fluid infusion (eg. with dextrose)
  - primary polydipsia
  - absorption of irrigant (eg. during transurethral prostatectomy)
  - freshwater drowning
  - beer potomania (with low solute intake)

- Impaired water excretion
  - syndrome of inappropriate antidiuretic hormone secretion
  - reset osmostat syndrome
  - renal failure
  - glucocorticoid deficiency
  - hypothyroidism

- Shift of water from intracellular to extracellular space, caused by osmotically active substances eg.
  - Glucose
  - Urea
  - Mannitol.

3. Water and sodium excess
   - cardiac failure
   - hepatic failure
   - nephrotic syndrome
   - renal failure.

Drugs are a common cause of hyponatraemia: they can cause hyponatraemia via a number of different mechanisms. The most frequently implicated are:
   - antipsychotics
   - carbamazepine
   - diuretics
   - non-steroidal anti-inflammatries
   - selective serotonin reuptake inhibitors.

Others include:
   - angiotensin-converting enzyme inhibitors
   - angiotensin-II receptor antagonists
   - amiodarone
   - clofibrate
   - colchicine
   - cyclophosphamide
   - DDAVP
   - dopamine agonists
   - melphalan
   - opiates
   - oxytocin

- proton pump inhibitors
- sulphonylureas
- theophylline
- tricyclic antidepressants.

7.2.2 Investigation

- History and clinical examination usually reveals the cause of hyponatraemia in most cases. A full drug history is important to exclude medications as a cause of hyponatraemia. Further investigations may be required if the cause is not obvious.
- Serum osmolality is useful in hyponatraemia. In true hyponatraemia it will be low. Increased osmolality with hyponatraemia suggests the presence of another osmotically active substance such as glucose or mannitol. If increased osmolality is found plasma [glucose] should be measured on the sample. Normal osmolality is found in hyponatraemia secondary to interference in measurement from hyperproteinaemia or lipaemia, in which case the serum [total protein], [triglyceride] and [cholesterol] can be measured. In this case [sodium] could be measured via a direct ISE method (usually a point-of-care blood gas analyser), which is not affected by hyperproteinaemia or lipaemia.
- Urine osmolality can help elucidate the cause of hyponatramia. If the urine osmolality is <100 mOsm/kg consider causes of excess water intake such as primary polydipsia, inappropriate IV fluid administration and beer potamania.
- Urine is less than maximally dilute (> 100 mOsm/kg) in the syndrome of inappropriate antidiuresis (SIAD). In SIAD the urine sodium is typically >30 mmol/L. Diagnosis of SIAD can only be made if other causes of impaired water excretion are excluded (renal failure, medications, adrenal failure, hypothyroidism).
- Any condition causing increased secretion of ADH (conditions causing decreased intravascular volume or increased plasma osmolality) will have a similar effect on urine osmolality. A low urine [sodium] (<30 mmol/L) in this situation suggests intravascular hypovolaemia, including conditions such as heart failure, liver failure and nephrotic syndrome where the intravascular volume may be depleted, despite an expanded ECF volume.
- A urine [sodium] is occasionally helpful to confirm appropriate retention of sodium in hypovolaemic patients with normal kidney function when urine sodium should be <20 mmol/L.
- If urine sodium is >30 mmol/L consider causes of renal loss of sodium.
- If the patient is on diuretic(s) interpretation of urine [sodium] is unreliable, in this case hyponatraemia may be due to the diuretic, but all other causes of hyponatraemia should be considered.
- Other investigations may exclude or suggest causes of hyponatraemia. Serum [urea] and [creatinine] can be used as part of the assessment of renal function. A raised [urea] in conjunction with clinical signs may suggest a decreased extracellular fluid volume. Potassium is usually measured at the same time as sodium; adrenal insufficiency may be suspected if the [potassium] is raised (in conjunction with clinical information suggesting adrenal insufficiency). A short tetracoactide

(Synacthen) test is used to diagnose adrenal insufficiency. TSH and free T4 can be measured to exclude primary or secondary hypothyroidism, rare causes of hyponatraemia.

7.3 Notes

1. The cause of either hypo- or hyper-natraemia is often multifactorial.
2. The rate of change of [sodium], usually determines the severity of the clinical symptoms and signs. Patients with rapidly changing sodium (>10 mmol/L over days), symptomatic patients or those with a sodium < 115 mmol/L should be managed in secondary care under close supervisiion.
3. In managing patients with chronic hypo- or hyper-natraemia it is essential to avoid over rapid correction, as the intracellular shifts in osmolality can lead to cell damage in the central nervous system (central pontine myelinolysis).
4. Laboratories should establish polices for phoning abnormal sodium results to an appropriate medical officer.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions.

Measurement of [sodium] is not used alone for diagnosis of specific conditions.

9 Systematic reviews and guidelines

9.1 Systematic reviews

None identified as directly relevant.

9.2 Guidelines

Hyponatraemia

1. National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries. Hyponatraemia 2011. http://cks.nice.org.uk/hyponatraemia (accessed 5.viii.2013)
2. Guidelines and Audit Implementation Network (GAIN). Hyponatraemia in adults 2010. http://www.gain-ni.org/images/Uploads/Guidelines/Hyponatraemia_guideline.pdf (accessed 5.viii.2013)
3. National Institute for Health and Care Excellence (NICE). Intravenous fluid therapy in adults in hospital. (Clinical guideline 174.) 2013 www.nice.org.uk/CG174 (accessed 3.i.2014)
4. British Medical Journal (BMJ). Intravenous fluid therapy in adults in hospital: summary of NICE guidance BMJ 2013;347:f7073.
5. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Euor J Clin Endocrinol 2014;170:G1-G47.

9.3 Recommendations

Hyponatraemia

1. Sterns RH. Overview of the treatment of hyponatraemia. UpToDate 2013.
http://www.uptodate.com/contents/overview-of-the-treatment-of-hyponatremia (accessed 27.xi.2013)

Hypernatraemia

1. Sterns RH. Treatment of hypernatremia. UpToDate 2013.
http://www.uptodate.com/contents/treatment-of-hypernatremia (accessed 27.xi.2013)
2. Lukitsch I, Batuman V. Medscape 2012.
http://emedicine.medscape.com/article/241094-overview (accessed 27.xi.2013)

10 Links

10.1 Related analytes
None

10.2 Related tests
Usually requested as part of 'urea and electrolytes' profile, which includes urea, creatinine, potassium and sodium.
Serum and urine osmolality, and urine sodium can be useful additional tests to help determine the cause of abnormal serum sodium concentrations.

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Date Completed: 3.2014
Date Revised: