Measurement of plasma/serum sodium concentration is one of the most frequently requested blood tests in clinical practice.

Although usually performed in the laboratory, the test is also available at the point of care using technology incorporated into blood gas and other point-of-care analyzers.

In health, sodium concentration is maintained between 135 and 145 mmol/L, so that hyponatremia (reduction in plasma sodium) is diagnosed if the concentration falls below 135 mmol/L.

Effective, safe correction of plasma sodium depends on establishing the cause. Initial assessment of the hyponatremic patient should include due consideration of the rare possibility that the result is spuriously low: that this is not true hyponatremia but so-called “pseudo”hyponatremia.

The main purpose of this article is to outline how some laboratory methods can, in certain well-defined clinical situations, give rise to a falsely low plasma sodium concentration, and thereby a diagnosis of pseudohyponatremia.

Indicators that help establish a diagnosis of pseudohyponatremia will be discussed, and with the help of two published case histories, the danger of failing to recognize pseudohyponatremia will be highlighted.

The article begins, however, with a brief overview of normal sodium metabolism and hyponatremia.

The adult human body contains around 3500 mmol (80 g) of sodium. Just under 30% is contained in a non-exchangeable state in bones.

The remaining (exchangeable) sodium is divided unevenly between extracellular fluid (ECF), which includes blood plasma, and intracellular fluid (ICF).

The energy-dependent sodium pump, present in the membrane of all cells, which effectively pumps sodium out of cells in exchange for potassium, ensures the large differential in sodium concentration between the ICF (5-10 mmol/L) and ECF (135-145 mmol/L) concentration.
Regulation of sodium and water balance

Sodium is involved in the process of neuromuscular transmission and the vital process that maintains normal blood (ECF) volume. This second function, which operates in part through the determining effect that plasma sodium concentration has on plasma osmolality, reflects the interrelatedness of sodium and water metabolism. Maintenance of normal plasma sodium concentration, a requirement for both functions, is dependent on a normal regulation of both sodium and water balance.

A minimum of 10-20 mmol of sodium is inevitably lost from the body each day in sweat, feces and urine. This must be replaced to maintain balance. In fact, we ingest far more than this. An average diet contains between 100 and 200 mmol of sodium, predominantly as salt flavoring. Excess sodium is excreted by the kidneys in urine, so that it is the renal regulation of sodium excretion, mediated in part by the adrenal hormone aldosterone, that ensures the sodium balance, despite wide variation in both sodium intake and extrarenal loss of sodium.

By regulating the urine volume, the kidneys also play a major role in maintaining the water balance. Under the influence of the pituitary hormone vasopressin (alternate name antidiuretic hormone, ADH) released in response to rising plasma osmolarity consequent on water deficit, the kidneys appropriately retain water and excrete concentrated urine of low volume. Unlike sodium intake, water intake is regulated. The mechanism of this regulation is the thirst response, which is also induced by rising plasma osmolarity. This powerful mechanism that ensures appropriate fluid intake is as significant as the renal mechanisms that ensure appropriate water loss, the for maintenance of a normal water balance.

Hyponatremia - Causes, consequences and treatment options

Hyponatremia is a relatively common finding among surgical patients during the postoperative period and also among patients suffering a range of medical conditions. In fact, it is the single most common disturbance of blood chemistry, affecting 15 % of hospitalized patients in one UK survey [1]. In the majority of cases, hyponatremia is mild (in the range of 130-135 mmol/L), self-limiting and not associated with symptoms. However, some suffer severe hyponatremia, usually defined as plasma sodium less than 125 mmol/L. This is a potentially serious acute condition associated with significant neurological symptoms.

The concentration of plasma sodium is dependent on two variables: the amount of sodium in the ECF and the amount of water in the ECF (i.e. ECF volume). Although it might be supposed that hyponatremia is associated with sodium deficiency, this is not always the case. Indeed, hyponatremia is much more commonly due to an excess of water in the ECF than to a deficit of sodium. Depending on its cause, hyponatremia can be associated with a normal total amount of sodium, sodium deficit or even sodium excess.

All cases of hyponatremia can be assigned to one of three groups, depending on the clinically assessed fluid status of the affected hyponatremic patient [2]. These three groups are:

- hypovolemic hyponatremia (hyponatremia associated with clinical evidence of fluid depletion)
- euvoelastic hyponatremia (hyponatremia associated with only mild [clinically undetectable] increased fluid status) or
- hypervolemic hyponatremia (hyponatremia in association with marked fluid excess, evident as edema)

Table 1 lists the most common causes of each of the three types of hyponatremia.

Severity of signs and symptoms due to hyponatremia depend on the degree of hyponatremia and the speed of onset. Those with mild hyponatremia (plasma sodium 130-135 mmol/L) almost invariably suffer no symptoms. Moderate hyponatremia (plasma sodium 125-130 mmol/L) may be associated with non-specific symptoms including headache, nausea and muscle cramps. More severe neurological symptoms including confusion, disorientation and hallucinations become progressively
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more likely as sodium falls below 125 mmol/L. The most severe presentation occurs in those with acute onset (within 48 hours of plasma sodium <115 mmol/L). These patients may suffer seizures and lapse into coma. The risk of a fatal outcome increases as sodium falls below 115 mmol/L.

Crucially, treatment of hyponatremia depends on the severity and a clear understanding of the mechanism of hyponatremia in each case. No treatment may be appropriate, but for those that do require treatment, the options include intravenous administration of isotonic or hypotonic saline solutions, fluid restriction or diuretic therapy [3]. Withdrawal of diuretic drugs may be necessary. Inappropriate choice of treatment can have serious effects and may contribute to fatal outcome [4].

Methods used to measure plasma sodium concentration

Pseudohyponatremia is defined as a spuriously low plasma sodium concentration; the measured sodium concentration is low, but the true physiological plasma sodium concentration is normal. The related condition pseudonormonatremia is diagnosed if the measured sodium concentration is normal but the true plasma sodium concentration is raised. Since the error that pseudohyponatremia and pseudonormonatremia represent is due to the method used to measure plasma sodium concentration, it would be helpful to briefly review this methodology. Historically, plasma sodium measurement has been made using one of two basic techniques:
• Flame emission spectrophotometry (FES)
• Ion-specific electrode (ISE) potentiometry

For thirty years until around 1980, FES was the sole method available for routine measurement of plasma sodium. The technique [5] involves aspirating a fine (atomized) spray of a diluted plasma or serum sample into a flame, thereby changing the color of the flame. The intensity of the emitted light at the wavelength characteristic of sodium (539 nm) is measured. This measured emission intensity is directly proportional to the number of sodium atoms in solution. By comparing the measured intensity of the sample with that of standard solutions of a known concentration, the sodium concentration of the plasma sample can be computed. Although it remains a reference method, FES has been largely replaced by the alternative, more convenient ISE methodology. Only a small minority of laboratories still use FES.

Potentiometric (ISE) measurement depends on the potential difference (measured in mV) that is generated between a reference electrode and measuring electrode when the measuring electrode is exposed to ions in solution. The use of standard solutions of a known concentration allows computation of concentration in the test solution from the measured mV. An ion-selective electrode is one in which the measuring electrode is able to respond only to a selected ion. Such selectivity allows measurement of a single ion (e.g. sodium Na+) in a solution (e.g. plasma) containing many ionic species; the measured potential difference is due solely to the activity of the particular ionic species. In the clinical laboratory two ISE techniques are available for measurement of plasma sodium concentration: direct ISE and indirect ISE [6]. The only difference between the two is that in the first case (direct ISE) the sample is presented undiluted to the electrode, whereas in the second case the sample is first diluted in a buffer. Of the two techniques indirect ISE is the more widely used. An advantage of diluting the sample is that the measured activity approximates more closely to the concentration, and consequently indirect ISE results match those obtained using the historical reference FES method [7]. A 2003 survey [8] revealed that two thirds of US laboratories were using indirect ISE, nearly all of the rest were using direct ISE and <1 % continued to use FES. Point-of-care measurement of sodium is almost exclusively made using direct ISE. This is the technology incorporated into blood gas analyzers. Direct ISE allows measurement of plasma sodium directly from a whole-blood sample.

Pseudohyponatremia is only associated with methods in which the sample is prediluted, i.e. FES and indirect ISE. One of the principal advantages of direct ISE as a technique for sodium measurement is that the sample is presented undiluted to the electrode and is therefore never associated with either pseudohyponatremia or pseudonormonatremia. How, then, does sample dilution give rise to pseudohyponatremia?

**Pseudohyponatremia - the electrolyte exclusion effect**

In health, water accounts for 93 % of the blood plasma volume, the remaining 7 % is occupied by dissolved solids, mostly proteins and lipids [9]. Sodium, indeed all plasma electrolytes are present only in the aqueous phase. The exclusion of sodium from the non-aqueous (solids) portion of plasma is central to an understanding of why predilution of plasma can lead to pseudohyponatremia.

Plasma sodium results are expressed as mmol per liter (mmol/L) of plasma, but sodium is present only in the water fraction of plasma; it is the concentration of sodium in plasma water that is the important physiologically relevant parameter. Suppose a sample gives a sodium concentration of 140 mmol/L and water comprises 93 % of the total plasma volume, then the physiologically relevant sodium in the plasma water concentration is 140 × (100 / 93) = 150 mmol/L. So long as the water content of plasma remains constant, this difference between plasma sodium concentration and plasma water sodium concentration is predictable and can therefore be ignored. A problem, however, arises if the water content of plasma deviates from normal, and samples are prediluted prior to measurement.

Consider two patients, A and B. They both have the same concentration of sodium in plasma water (150 mmol/L) but their % plasma water content is different. Patient
A is normal in this respect; 93 % of his plasma volume is occupied by water and 7 % by solids. The plasma of patient B, by contrast, is abnormal, comprising 80 % water and 20 % solids. Plasma A and Plasma B are diluted 1:10 and the sodium concentration measured.

**EXAMPLE, Patient A**

1 mL plasma A from patient A contains:

- 930 µL water and 70 µL solid
  - \([\text{Na}^+]\) in water = 150 mmol/L
  - \([\text{Na}^+]\) in solid = 0 mmol/L

Measured sodium concentration of 1:10 diluted plasma = 150 × 0.93/10 = 13.95 mmol/L

Plasma sodium concentration = 13.95 × 10 = 140 mmol/L

**EXAMPLE, Patient B**

1 mL plasma B from patient B contains:

- 800 µL water and 200 µL solid
  - \([\text{Na}^+]\) in water = 150 mmol/L
  - \([\text{Na}^+]\) in solid = 0 mmol/L

Measured sodium concentration of 1:10 diluted plasma = 150 × 0.8 / 10 = 12 mmol/L

Plasma sodium concentration = 12 × 10 = 120 mmol/L

Although both patients have the same (normal) concentration of sodium in plasma water, the plasma sodium concentration following dilution is normal in Patient A, but grossly abnormal (hyponatremic) in Patient B. If plasma sodium of both A and B had been measured using direct ISE technology, results would have been the same and normal because this technique measures the sodium activity (concentration) in plasma water directly. Patient B has pseudohyponatremia, i.e. a physiologically normal plasma water sodium concentration, but a reduced measured plasma sodium concentration.

**Pseudohyponatremia and dissolved solids**

As outlined above it is the abnormally decreased proportion of water to solids in plasma that gives rise to pseudohyponatremia. Since the solid material in blood plasma is composed largely of protein and lipids, it is perhaps not surprising that there is a relationship that allows calculation of the % water content of plasma from the concentration of plasma lipids and plasma proteins [10], namely:

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\text{Plasma water \% } = 99.1 - (1.03 \times \text{lipid concentration g/L}) - (0.73 \times \text{protein concentration g/L})
\]

As the lipid or protein concentration increases, the plasma water content decreases and the error that pseudohyponatremia represents becomes ever larger. Significant pseudohyponatremia (or pseudonormonatremia) can occur in any clinical situation in which the serum lipid (triglyceride or cholesterol) or protein concentration is markedly increased. Most commonly, it is caused by severe hypertriglyceridemia (serum triglyceride usually >1500 mg/dL or >17 mmol/L) and, less commonly, by severe hyperproteinemia (serum protein usually >10 g/dL or >100 g/L) [11]. Conditions that may be associated with hyperlipidemia of sufficient severity to cause pseudohyponatremia include diabetes [12], obstructive liver disease [13], nephritic syndrome, acute pancreatitis [14] and familial (inherited) hypertriglyceridemia [12]. The only pathological conditions that are associated with an increase in the serum protein concentration of sufficient severity to cause pseudohyponatremia are a group of disorders called the paraproteinemias; multiple myeloma is the most common [11]. Therapeutic use of high-dose IV-administered immunoglobulins can cause pseudohyponatremia [15].

**Establishing or excluding a diagnosis of pseudohyponatremia**

The first consideration when a patient presents with a reduced serum/plasma sodium concentration is the method of measurement. If the determination was made using direct ISE, then pseudohyponatremia is immediately
excluded. If the method of measurement is indirect ISE or, much more rarely these days, FES, then pseudohyponatremia is a possibility that, however rare, must be excluded before treatment is considered. This is particularly important if the plasma is lipemic (turbid/milky due to the presence of excess lipid) rather than of normal clarity, or the apparent hyponatremia is discovered in the context of clinical conditions such as diabetes and multiple myeloma that can give rise to pseudohyponatremia. Clearly, repeat measurement using direct ISE technology is the most reliable way forward. If the sodium result by direct ISE is normal, pseudohyponatremia is confirmed. If the direct ISE result matches that obtained by indirect ISE, then pseudohyponatremia is reliably excluded.

If direct ISE is not available, simultaneous calculation and measurement of plasma osmolarity is very useful [3]. Measured osmolarity is normal in pseudohyponatremia but calculated osmolarity – based as it is on a erroneously low plasma sodium result – is reduced. An increased osmolar gap (i.e. the difference between measured and calculated osmolarity) suggests pseudohyponatremia.

If plasma triglyceride, cholesterol and total protein values for the sample are available, then it is possible to calculate the % water content of serum (see above). Reduced % water content (<93 %) indicates pseudohyponatremia.

Failure to recognize pseudohyponatremia can have serious consequences

Two illustrative case studies

Pseudohyponatremia is an artefact that should not be treated. The following two case studies [16,14] demonstrate the potential dangers of failing to recognize pseudohyponatremia and treating it as if it were “true” hyponatremia. The first case [16] concerns a 6-year-old, insulin-dependent diabetic boy who was admitted to hospital in a comatose and dehydrated state following two weeks of intermittent vomiting and abdominal pain. Ophthalmoscopic examination revealed an abnormality of the eyes (lipemia retinalis) that is caused by severe hyperlipidemia. Blood testing revealed metabolic acidosis, severe hyperglycemia (blood glucose 37 mmol/L) and severe hyponatremia (serum sodium 89 mmol/L). The laboratory reported that the serum was “strikingly lipemic”. Subsequent analysis of this admission sample revealed that the serum triglyceride concentration was 223 mmol/L and the cholesterol concentration 41.4 mmol/L. No connection was made between the severe hyperlipidemia and hyponatremia. Since pseudohyponatremia was not recognized, the apparent hyponatremia was treated inappropriately with 0.9 % saline, beginning 2 hours after admission. As a result of the saline treatment, serum sodium increased to 116 mmol/L at 7 hours after admission, but there was clinical evidence (right hemiplegia and tonic convulsions) of evolving brain damage. The child’s condition deteriorated and he died 33 hours after admission due to brain hemorrhage. The 7-hour postadmission serum sample with apparent sodium of 116 mmol/L was treated to remove the lipids and reanalyzed. The true serum sodium was found to be 222 mmol/L. The inappropriate treatment had caused very severe hypernatremia, which almost certainly contributed to the boy’s death.

Quite apart from its cautionary value, this case history highlights the potential for pseudohyponatremia in those suffering the severe metabolic effect of insulin deficiency known as diabetic ketoacidosis (DKA). Hyperlipidemia is a common feature of DKA, and in a small minority of these patients, including this young boy, hyperlipidemia is of sufficient severity to cause pseudohyponatremia.

Failure to recognize pseudohyponatremia led to florid psychiatric symptoms, including apparent suicidal intent in a 40-year-old woman with severe acute pancreatitis [14]. Her plasma sodium on admission was 111 mmol/L. Despite evidence of severe hyperlipidemia, including very lipemic serum, serum cholesterol level of 732 mg/L and triglyceride level of 4130 mg/dL, the possibility that the sodium concentration was spuriously low was not considered. Instead, the apparent hyponatremia was assumed to be related to her near-fatal hypotensive state (blood pressure was imperceptible on admission), and treated aggressively. Over the first 5 days of her hospital stay she was continuously given large quantities of hypertonic and isotonic saline solutions IV until her
measured plasma sodium was within the normal range. In fact, the actual plasma water sodium concentration at this point was probably close to 200 mmol/L; she was by now severely hypernatremic, although those caring for her were unaware that this was the case. Over the 5-day period the symptomatic effect of this unrecognized worsening hypernatremia was evident. The patient became "uncooperative, argumentative and finally irrational". She complained of severe thirst and demanded water when her care plan included nil by mouth. In desperation she drank a bowl of soapy bath water. Her disturbed mental state consequent on the still unrecognized severe hypernatremia led her to attempt to jump from the upper-story window of the intensive care unit where she was being treated. A psychiatric consult resulted in sedation and physical restraint.

Eventually on the 6th day of her hospital stay, two consultants with specialist interest in metabolism reviewed her case and both independently recognized that the initial sodium measurement was spuriously low due to the presence of lipids – pseudohyponatremia was now diagnosed. Intravenous administration of sodium was immediately stopped and the patient was allowed free access to water. Her mental status soon returned to normal as the iatrogenic hypernatremia resolved, and she eventually recovered from the acute episode of pancreatitis that brought her to hospital.

**Summary**

A reduced plasma sodium concentration is called hyponatremia. Pseudohyponatremia is an artefact; measured serum sodium is reduced but actual plasma sodium is normal. The condition can only arise if the serum lipid or protein concentration is markedly increased and plasma sodium is measured using either indirect ISE or flame photometer. Both of these methods of analysis involve predilution of serum sample. Direct ISE methods, used in point-of-care analyzers (including blood gas analyzers) for measurement of serum sodium do not involve a dilution step. This difference ensures that pseudohyponatremia cannot occur if direct ISE is used to measure the plasma sodium concentration. It is rare for the serum lipid or serum protein concentration to rise to the extreme levels sufficient to cause pseudohyponatremia, so pseudohyponatremia is a rare occurrence. Still, it is vital that when it occurs, pseudohyponatremia is recognized as the artefact it is, and not treated. Failure to recognize pseudohyponatremia can have serious, perhaps fatal consequences if the "apparent" hyponatremia is treated. There is some evidence in the literature [17, 18] to suggest that some clinicians believe that with the demise of flame photometry and the emergence of ISE technology, pseudohyponatremia is no longer a problem. That is not the case. The majority of clinical laboratories use indirect ISE for the measurement of serum sodium and this is as prone to pseudohyponatremia as the older flame photometric method. Only universal adoption of direct ISE methods will finally eradicate the problem of pseudohyponatremia.
References

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