

Spurious Electrolyte Disorders: A Diagnostic Challenge for Clinicians

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Key Words

Ion-selective electrodes · Pseudohyperkalemia ·
Pseudohyperphosphatemia · Pseudohypocalcemia ·
Pseudohyponatremia · Pseudohypomagnesemia

Abstract

Spurious electrolyte disorders refer to an artifactually elevated or decreased serum electrolyte values that do not correspond to their actual systemic levels. When a clinician is confronted with a case of electrolyte disturbance, the first question should be whether it is an artifact. Spurious electrolyte disorders (pseudohyponatremia, pseudohypernatremia, pseudohypokalemia, pseudohyperkalemia, pseudohypomagnesemia, pseudohypophosphatemia, pseudohyperphosphatemia, pseudohypocalcemia and pseudohypercalcemia) are not infrequently observed in clinical practice. The recognition that an electrolyte disturbance may be an artifact may prevent inappropriate therapeutic interventions that could potentially have unfavorable outcomes. Clinicians must be alert to the possibility of spurious laboratory abnormalities when faced with conflicting laboratory values or measurements that are discordant with the clinical presentation. Moreover, in the presence of conditions that predispose to spurious electrolyte disorders, the normal measured electrolyte levels should raise the suspicion that true electrolyte disorders may be present.

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Introduction

Electrolyte disorders are common in clinical practice [1, 2]. They are mainly encountered in hospital populations occurring in a broad spectrum of patients from asymptomatic to critically ill. There are several deleterious effects associated with electrolyte disturbances and their treatment.

The evaluation of the etiology of electrolyte disorders is mandatory before initiating specific therapy [3]. First, one should verify that these disorders are not an artifact and, thus, further investigation of the underlying cause is not required. This will also help avoid inappropriate management that can lead to adverse outcomes.

Spurious electrolyte disorders refer to an artifactually elevated or decreased serum electrolyte values that do not correspond to their actual systemic levels. Patients with these disorders do not exhibit symptoms or signs of a given electrolyte disturbance, and no treatment is needed. Clinicians must be wary of laboratory artifacts and remember to correlate the laboratory values with the clinical presentation of the patient. Moreover, in the presence of conditions that predispose to spurious electrolyte disorders, the normal measured electrolyte levels should raise the suspicion that true electrolyte disorders may be present.

Table 1. Principal causes of spurious electrolyte disorders

1. Sodium disorders^a

Pseudohyponatremia (the effective serum osmolality is normal)

- Marked hyperlipidemia (hypertriglyceridemia, hypercholesterolemia)
- Hyperproteinemia (paraproteinemia, hypergammaglobulinemia or intravenous immunoglobulin administration)

Pseudonormonatremia (true hyponatremia and hypertonicity may be present)

- Hyperproteinemia or hyperlipidemia

Pseudohyponatremia

- Severe hypoproteinemia
-

2. Potassium disorders

Pseudohypokalemia

- Blood specimens with a very high white cell count ($>100,000/\mu\text{l}$) kept at room temperature for prolonged period
- Blood samples from patients recently administered intravenous insulin stored at room temperature for prolonged period
- Delayed transport of venous blood specimens over periods of high ambient temperature (seasonal pseudohypokalemia)

Pseudohyperkalemia (serum K^+ exceeds the plasma K^+ by more than 0.3 mEq/l)

- Tight tourniquet application in combination with excessive arm exercise prior to venipuncture
- Mechanical trauma during venipuncture (hemolysis)
- Centrifugation of samples before the complete clot formation
- Marked leukocytosis (white cell count $>70,000/\text{mm}^3$) or thrombocytosis (platelet count $>500,000/\text{mm}^3$)
- Familial pseudohyperkalemia or hereditary spherocytosis

Reverse pseudohyperkalemia (falsely elevated plasma K^+ levels that are higher than serum levels)

- Massive leukocytosis when heparin is used as anticoagulant in plasma tubes
 - Pneumatic tube transport of the leukemic specimen
-

3. Calcium disorders

Pseudohypocalcemia

- Hypoalbuminemia^b
- Gadolinium-based contrast agents (gadodiamide, gadoversetamide)

Pseudohypercalcemia

- Hyperalbuminemia^b, thrombocytosis, Waldenström's macroglobulinemia multiple myeloma
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4. Phosphate disorders

Pseudohypophosphatemia

- Mannitol administration

Pseudohyperphosphatemia

- Hyperglobulinemia (multiple myeloma, Waldenström's macroglobulinemia, monoclonal gammopathy)
 - Hyperbilirubinemia
 - Hyperlipidemia
 - High dose of liposomal amphotericin B
 - Sample contamination with recombinant tissue plasminogen activator or heparin
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5. Hypomagnesemia

- Hypoalbuminemia
-

^a Spurious sodium disorders occur when sodium is measured with indirect ISE.

^b The ionized serum calcium levels are normal.

Consequently, the knowledge of the potential existence of spurious electrolyte disturbances, the underlying disorders as well as the possible pathogenetic mechanisms may improve the management of patients.

We review the main spurious electrolyte disorders (table 1) and discuss the underlying mechanisms.

Pseudohyponatremia

Hyponatremia is the most common electrolyte disorder in clinical practice [1]. The initial approach to the hyponatremic patient is to measure the serum osmolality to determine whether the hyponatremia represents a true

hypo-osmolar state [3]. Indeed, in a patient with hyponatremia normal effective serum osmolality (measured as serum osmolality less serum urea level in millimoles per liter) suggests the presence of pseudohyponatremia. Hyperglycemia, mannitol administration, the presence of alcohol or azotemia as well as the use of solutions containing glycine, sorbitol, or mannitol in patients undergoing transurethral resection of the prostate or bladder are also associated with low serum sodium and normal (or increased) serum osmolality.

In normal individuals, serum is composed of water (approximately 93%), with fats and proteins (nonaqueous or solid phase) accounting for the remaining 7%. Sodium is located in the serum water phase only. Serum water fraction may fall below 80% in patients with marked hyperlipidemia or hyperproteinemia. In these settings, the serum sodium concentration, measured per liter of serum, not serum water, is artifactually reduced (pseudohyponatremia) [4, 5]. However, the physiologically important serum water and sodium as well as serum osmolality remain unaffected. There are two methods using ion-selective electrodes (ISE) for the measurement of serum electrolytes (direct ISE and indirect ISE). Only the indirect ISE is prone to pseudohyponatremia when the serum water content is less than 93% because it dilutes the serum samples, before measuring the electrolyte concentration, with a predetermined volume of ionic solution. The concentration of the electrolyte is then adjusted by a fixed factor of 0.93 (the average volume water in serum) to obtain the actual ion concentration in serum [6]. In contrast, direct ISE, not including a predilution step, is not susceptible to pseudohyponatremia [4, 7]. Direct ISE is now readily available at most hospitals given that most bedside electrolyte analyzers use this method. In lipemic or hyperproteinemic samples, when the direct ISE is not available, the corrected sodium concentration should be determined as an alternative by using the following equation: corrected sodium value = (indirect sodium value $\times$ 0.93)/calculated serum water fraction.

The water content of serum in patients with hyperlipidemia or hyperproteinemia can be estimated from the following formula: serum water content (%) = $99.1 - (0.001 \times \text{lipid concentration in mg/dl}) - (0.7 \times \text{protein concentration in g/dl})$ [4].

The computation of the serum water fraction by using this formula should be considered as an approximation at best taking into account that its validity has been questioned [6]. A diagnostic algorithm for suspected pseudohyponatremia is provided in figure 1.

Hyperproteinemia (e.g. due to paraproteinemia, hypergammaglobulinemia or intravenous immunoglobulin administration) is also associated with spurious hyponatremia [4, 5, 8, 9]. Another cause of pseudohyponatremia associated with hyperproteinemia is the error produced by hyperviscosity when the sample is aspirated and less than the expected volume is obtained. In addition, sporadic errors of electrolyte measurement occur when high globulins exist as a result of unexpected precipitation of the sample with various diluents [10].

Distinguishing true hyponatremia from pseudohyponatremia is clinically critical, as treatment aimed at increasing serum sodium concentration in patients with pseudohyponatremia may lead to adverse outcomes [11].

The presence of normal serum sodium levels in a patient with hyperproteinemia or hyperlipidemia should alert clinicians to the possibility that hypernatremia and hypertonicity may be present (pseudonormonatremia). The opposite phenomenon of pseudohypernatremia (as well as pseudonormonatremia) may also occur when sodium is measured with indirect ISE, as a result of severe hypoproteinemia [12–14]. It has been recently reported that in hypoalbuminemic states indirect ISE is associated with a sodium overestimation (up to 10 mEq/l) as compared to direct ISE [15].

Undoubtedly, in clinical conditions characterized by hypo- or hyperproteinemia and hyperlipidemia, indirect ISE can lead to misclassification of pseudohyponatremia, pseudonormonatremia, or pseudohypernatremia. In such cases, the measurement of serum sodium concentration by direct ISE is fully warranted to avoid inappropriate fluid and electrolyte management with potentially adverse outcome.

Pseudohypokalemia

In vivo translocation of potassium (K^+) from the extracellular fluid into the cells can lead to pseudohypokalemia. In leukemic patients with a very high white cell count ($>100,000/\mu\text{l}$), the K^+ movement into leukocytes may result in spurious hypokalemia if blood samples are stored for prolonged period at room temperature [16]. In fact, these patients may have a relatively normal plasma concentration, but the measured value may be below 1.0 mEq/l (without any symptoms) [17]. The recent administration of intravenous insulin is also associated with pseudohypokalemia if blood specimens are allowed to stand at room temperature due to insulin-mediated K^+ shifts from the extracellular to intracellular compartment

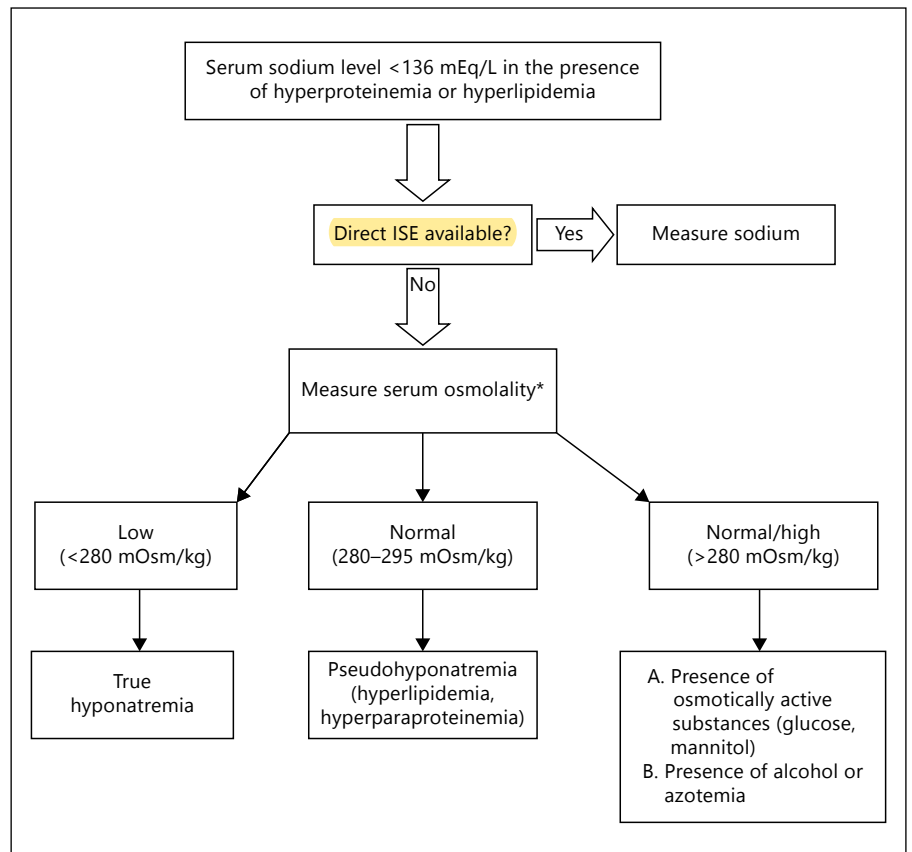


Fig. 1. Diagnostic algorithm for suspected pseudohyponatremia. Asterisk indicates that alternatively the corrected sodium concentration should be determined by using the following equation: corrected sodium = (indirect sodium $\times$ 0.93)/[99.1 – (0.001 $\times$ lipid concentration in mg/dl) – (0.7 $\times$ protein concentration in g/dl)].

[18]. Similarly, the cellular uptake of K^+ is the underlying mechanism of spurious hypokalemia in cases of delayed transport of blood samples over periods of high room temperature (seasonal pseudohypokalemia) [19, 20]. This in vitro phenomenon should be attributed to high temperature-induced enhanced sodium-potassium-exchanging ATPase activity [20].

The aforementioned problems of spurious hypokalemia can be avoided if the plasma or serum is rapidly separated from the cells or if the blood is stored at 4°C.

Pseudohyperkalemia

Hyperkalemia is a life-threatening condition that must be quickly recognized and treated because of the high risk of lethal arrhythmias and cardiac arrest [21]. On the other hand, identifying the presence of pseudohyperkalemia is crucial to avoid the complications caused by treating pseudohyperkalemia and thereby inducing actual hypokalemia. Pseudohyperkalemia is a well-recognized entity [22]. It is defined as an elevation in the measured K^+ con-

centration due to K^+ movement out of the cells (erythrocytes, leukocytes or platelets) either during or after drawing of the blood specimen. The presence of pseudohyperkalemia should be strongly suspected whenever hyperkalemia and hemolysis, extreme leukocytosis or thrombocytosis coexist. It should also be considered in the absence of apparent cause for the elevation in K^+ levels (impaired renal function, combination of K^+ raising drugs), in the absence of electrocardiogram changes and when there is no changes in muscle strength. It is worth mentioning that hyperkalemia is exceedingly rare if renal function is normal [23].

It is known that the serum K^+ concentration normally exceeds the true value in the plasma by 0.1 to as much as 0.5 mEq/l due to K^+ release from white cells and platelets during the clotting process [24]. Although this difference in normal subjects is clinically unimportant, the measured serum K^+ concentration may be falsely high (up to 9 mEq/l) in patients with marked leukocytosis (white cell count $>70,000/\text{mm}^3$) or thrombocytosis (platelet count $>500,000/\text{mm}^3$) [24–28]. With thrombocytosis, for example, the measured serum K^+ concentration rises by ap-

proximately 0.15 mEq/l for every 100,000/mm³ elevation in the platelet count [24]. In a retrospective series of 90 patients with thrombocytosis, pseudohyperkalemia (serum K⁺ >5.1 mEq/l) was observed in the majority of patients (n = 54, 60%) regardless of the cause of thrombocytosis [29]. Reactive or postsplenectomy thrombocytosis is sufficient to cause artificially high potassium levels [29, 30]. For example, rheumatoid arthritis, though infrequently, can induce pseudohyperkalemia possibly due to secondary thrombocytosis [31]. Pseudohyperkalemia should be diagnosed if the serum K⁺ exceeds the plasma K⁺ by more than 0.3 mEq/l. In such cases, the clinical decisions should be based on the plasma, not the serum K⁺ concentration.

Mechanical trauma during venipuncture (hemolysis) is the most common cause of pseudohyperkalemia. This condition is easily identified in the laboratory by the pink tinge to the plasma resulting from the release of hemoglobin from damaged red blood cells. Tight tourniquet application in combination with excessive arm exercise (e.g. an opening and closing hand) prior to venipuncture can induce a spurious elevation in K⁺ concentration by as much as 1–2 mEq/l [32]. However, a reddish serum may depict severe intravascular hemolysis rather than a hemolyzed specimen [33]. In such cases, the measured serum K⁺ may represent the true circulating value.

Spurious hyperkalemia may also be seen in familial pseudohyperkalemia, a rare autosomal dominant inherited disease, in which there is an abnormal red blood cell permeability leading to excessive K⁺ leakage. The defect is temperature dependent given that it occurs at low temperature (particularly below 20°C) but not at 37°C. The abnormal leak of potassium across the red cell membranes is thought to be passive and not mediated by changes in Na-K-ATPase activity [34]. This *in vitro* phenomenon of temperature-dependent leakage of potassium out of red blood cells also takes place in hereditary spherocytosis [35].

The phenomenon of reverse pseudohyperkalemia has also been described. Reverse pseudohyperkalemia is defined as falsely elevated plasma potassium levels that concurrently are higher than that found in serum [36]. It occurs in massive leukocytosis when heparin is used as the anticoagulant in the plasma tubes, possibly due to heparin-induced cell lysis [37]. Reverse pseudohyperkalemia is also ascribed to pneumatic tube transport of the specimen that can cause mechanical disruption of the malignant white blood cells [38]. Consequently, in the presence of substantial leukocytosis, clinicians need to be alert to the possibility of a spurious potassium result. In such cas-

es, improved preanalytical handling of the blood samples as well as the determination of potassium level by arterial blood gas (ABG) may lead to more accurate results. In fact, ABG analysis has been reported to be an extremely quick and reliable test due to the shorter interval between drawing of the sample and ABG analysis [39]. The superiority of arterial blood specimens as compared to venous blood specimens (even when a direct ISE is used) in assessing potassium levels in cases of extreme leukocytosis has also been shown [40]. This disparity should be ascribed to differences in mechanical stressors between venous and arterial blood draw techniques as well as to the fact that samples which are drawn from an arterial site and placed on ice are more rapidly analyzed for potassium [40].

Pseudohypocalcemia

The term pseudohypocalcemia refers to a reduction of total serum calcium concentration in the presence of a normal ionized serum calcium levels. Serum calcium exists in three forms: (1) free or ionized calcium, the physiologically active form that accounts for 50% of total serum calcium; (2) calcium complexed to anions, including bicarbonate, lactate, phosphate and citrate, and (3) calcium bound to plasma proteins, constituting the remaining 40%. Approximately 80% of the protein-bound calcium fraction is associated with albumin [41]. Therefore, a patient with abnormally high serum albumin will have proportionally elevated serum calcium, whereas the reported serum calcium in a patient with low serum albumin will be less than the true value. In such cases, however, the ionized serum calcium levels are normal. In hypoalbuminemic states, one of the commonly used formulas to correct total calcium levels is by adding 0.8 mg/dl (0.2 mmol/l) to measured calcium values for every 1 g/dl decrease in serum albumin from normal value (assumed to be 4 g/dl). Given that the accuracy of this method is poor (particularly among critically ill and geriatric patients), the biologically important ionized calcium concentration should be measured when possible [42, 43].

The gadolinium-based contrast agents gadodiamide and gadoversetamide may interfere with the colorimetric assays for calcium leading to spurious hypocalcemia. With the exception of patients with impaired renal function who may retain the contrast agent for prolonged periods, this type of hypocalcemia is rapidly reversible as the gadolinium is excreted in the urine [44, 45]. In a series of 896 patients whose serum calcium concentration was de-

terminated within 24 h of gadodiamide administration, 165 (18.4%) patients exhibited pseudohypocalcemia. Furthermore, a marked decrease in the measured calcium levels [<6 mg/dl (1.5 mmol/l)] was detected in 25 (2.8%) patients. The calcium concentration was correlated with serum creatinine ($r = 0.39$, $p < 0.001$), gadodiamide dose ($r = 0.37$, $p < 0.001$), and time between gadodiamide administration and phlebotomy ($r = -0.28$, $p < 0.001$) [46]. Renal impairment, high-dose gadodiamide administration [i.e. ≥ 0.4 ml (0.2 mmol)/kg of body weight] and the blood draw shortly after the magnetic resonance imaging examination were associated with the largest serum calcium measurement errors [46]. Based on estimated glomerular filtration rate (eGFR), the recommended minimum waiting time from administration of contrast medium to collection of samples for the measurement of calcium varies considerably from 3 h (in patients with an eGFR of 130 ml/min) to 50 h (in patients with an eGFR of 20 ml/min) [47]. Pseudohypocalcemia does not take place when assays that employ atomic emission spectroscopy or ISE are used. Moreover, falsely lower serum calcium levels are not observed with other gadolinium-based agents such as dimeglumine gadopentetate, gadoteridol, or gadoterate meglumine [44, 45].

Pseudohypercalcemia

Pseudohypercalcemia is defined as an elevation of total serum calcium concentration in the presence of normal ionized serum calcium levels. Artifactual hypercalcemia is rarely observed in patients with hyperalbuminemia, thrombocytosis, Waldenström's macroglobulinemia and multiple myeloma [48]. Normally, about half the serum calcium concentration is bound to albumin. Therefore, in patients with elevations of serum albumin, mild hypercalcemia may be observed [49]. Under these circumstances, the corrected total calcium levels should be determined by subtracting 0.8 mg/dl (0.2 mmol/l) from the measured calcium values for every 1 g/dl increase in serum albumin from normal value (assumed to be 4 g/dl). In vitro release of calcium from activated platelets is the possible underlying mechanisms of spurious hypercalcemia in the setting of elevated platelet count [50]. Pseudohypercalcemia in patients with Waldenström's macroglobulinemia and multiple myeloma might be attributed to abnormal calcium binding by paraproteins. In addition, a hyperviscosity-associated interference in calcium measurements by an autoanalyzer may play a role [51–54].

Pseudohypophosphatemia

Mannitol is a nonreabsorbable polysaccharide that acts as an osmotic diuretic. Taking into consideration that this agent exerts only a weak phosphaturic effect is highly unlikely to cause significant hypophosphatemia per se. Thus, it should be mostly considered as a contributing factor in patients with low serum phosphate levels. On the other hand, mannitol treatment has been implicated as a cause of pseudohypophosphatemia. In fact, large doses of mannitol can induce pseudohypophosphatemia by binding to the molybdate used in the colorimetric assay of phosphorus. Falsely low serum phosphate values tend to occur in assays using relatively low concentrations of molybdate (Dupont end point method) [55–57].

Pseudohyperphosphatemia

Pseudohyperphosphatemia secondary to assay interference has been described in the setting of hyperglobulinemia (due to multiple myeloma, Waldenström's macroglobulinemia, or monoclonal gammopathy), hyperbilirubinemia, and hyperlipidemia [58–62]. In fact, extreme hyperphosphatemia of 31.6 mg/dl [10.2 mmol/l, normal values 2.5–4.3 mg/dl (0.8–1.4 mmol/l)] has been reported in a patient with multiple myeloma [63].

Furthermore, treatment with high dose of liposomal amphotericin B and sample contamination with recombinant tissue plasminogen activator or heparin have been implicated as causes of spurious hyperphosphatemia [64–66]. Liposomal amphotericin B-related pseudohyperphosphatemia is attributed to the interference of the drug in the Synchron LX-20 phosphorous assay. In such cases, normal values are found after removing the liposomal amphotericin B from the samples by ultrafiltration [65]. Alternatively, a different analyzer should be used for the accurate measurement of phosphate levels. Of note, phosphate-lowering interventions should be avoided in the presence of normal serum calcium and kidney function, given that in such cases true hyperphosphatemia is exceptionally infrequent.

Pseudohypomagnesemia

Apart from hypocalcemia, hypoalbuminemia is also associated with spurious hypomagnesemia. Consequently, in hypoalbuminemic states (serum albumin <4 g/dl)

corrected serum magnesium (Mg^{2+}) should be calculated using the formula: corrected Mg^{2+} (mEq/l) = measured Mg^{2+} (mEq/l) + $0.01 \times (40 - \text{albumin g/l})$ [67].

Conclusion

Spurious electrolyte disorders are frequently observed in clinical practice. The recognition that an electrolyte disturbance may be an artifact may prevent inappropriate

therapeutic interventions that could potentially have unfavorable outcome. Clinicians must be alert to the possibility of spurious laboratory abnormalities when confronted with conflicting laboratory values or measurements that are incompatible with clinical presentation.

Disclosure Statement

None related to this article.

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