

Spurious sodium results (2) pseudohypernatremia

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Plasma sodium concentration is measured with an ion-specific electrode (ISE) using either an undiluted sample (direct ISE) or diluted sample (indirect ISE). This is the second of two linked articles highlighting the **spurious sodium values that can occur if an indirect ISE method is used to analyze plasma samples with abnormal protein or lipid concentration**. The principal focus of the first article [1] was pseudohyponatremia, i.e. falsely reduced plasma sodium due to increased plasma protein or lipid concentration, but other topics relevant to both articles were discussed. In this second article we consider **pseudohypernatremia**, i.e. **falsely increased plasma sodium due to decreased plasma protein or lipid concentration**. The major focus of this second article is recent research that has revealed that pseudohypernatremia is a greater problem than previously recognized, particularly for critically ill patients. The case will be made for emerging expert opinion borne out of this research that, **for critically ill patients at least, plasma sodium should only be estimated using direct ISE techniques because they are unaffected by abnormal protein or lipid concentration**.

DEFINING PSEUDOHYPERNATREMIA

Plasma sodium concentration is normally maintained within the approximate reference range of 135-145 mmol/L so that hyponatremia (reduced plasma sodium) is diagnosed if result is <135 mmol/L, whilst hypernatremia (increased plasma sodium) is diagnosed if result is >145 mmol/L. **Pseudohypernatremia is defined as spuriously increased plasma sodium (>145 mmol/L) due to decreased plasma protein concentration**. Theoretically at least, decreased blood lipids would have the same effect but reduction in blood lipids of sufficient severity is extremely rare. Those with pseudohypernatremia are "truly" normonatremic.

The related term pseudonormonatremia is defined as spuriously normal plasma sodium concentration (135-145 mmol/L). This can occur if a patient with "true" hyponatremia has decreased protein concentration or if a patient with "true" hypernatremia has increased protein or lipid concentration. It is important to emphasize that the spurious sodium values that pseudohypernatremia and pseudonormonatremia represent only occur if the analysis method is indirect ISE.

The distinction between direct ISE and indirect ISE methodologies, and just why abnormal lipid/protein affects indirect ISE measurement but not direct ISE measurement is discussed in the linked article [1].

RECENT FOCUS ON PSEUDOHYPERNATREMIA AND PSEUDONORMONATREMIA

Historically, the principal focus of the effect that abnormal lipid and protein has on flame emission spectrophotometric (FES) and "indirect" ISE sodium measurement has been the pseudohyponatremia associated with increased plasma protein or lipid concentration [1]. The literature is replete with research/review articles and case history reports on pseudohyponatremia dating back to the 1950s, when the effect of raised lipids on FES sodium measurement was first described [2]. Despite the relative rarity of conditions that can give rise to pseudohyponatremia this preoccupation continues [3, 4] but in recent years there has been growing research interest in the pseudohypernatremia and pseudonormonatremia that result from reduced plasma protein concentration. Most of this work [5-8] has focused on the critically ill because hypoalbuminemia and therefore hypoproteinemia is a common feature of acute/critical illness; indeed, as this research has shown, is far more common than hyperproteinemia.

DECREASED PLASMA PROTEIN FAR MORE COMMON THAN INCREASED PLASMA PROTEIN

Chow *et al* [5] studied 190 unselected plasma samples collected over a 3-week period from patients in the critical care units of a UK hospital. All samples were submitted for sodium measurement by both "direct" and "indirect" ISE, as well as serum protein measurement. Hypoproteinemia (serum protein <60 g/L) was evident in 85 % of these samples; 13 % showed severe hypoproteinemia (<40 g/L). All the remaining samples had normal plasma protein (60-80 g/L). As would be predicted from a patient population with such a high prevalence of hypoproteinemia, the mean serum sodium determined by "indirect" ISE was significantly higher (140 mmol/L) than that obtained by "direct" ISE (136 mmol/L). A linear relationship was evident between serum protein concentration and the difference between "direct" and "indirect" ISE sodium results (Table I). Of the 190 paired sodium analyses, 19 % were hyponatremic (<135 mmol/L) by "direct" ISE but within normal range (135-145 mmol/L) by "indirect" ISE (i.e. cases of pseudonormonatremia); and 8 % were within the normal range by "direct" ISE but hypernatremic (>145 mmol/L) by "indirect" ISE (i.e. cases of pseudohypernatremia).

Serum protein (g/L)	Mean (SD) of difference between indirect and direct ISE (I-D) sodium results (mmol/L)
<40 (n=25)	4.72 ± 1.88
40-49 (n=68)	3.87 ± 1.84
50-59 (n=69)	3.24 ± 1.99
60-80 (n=28)	1.89 ± 1.73

TABLE I: Calculated difference between direct and indirect sodium measurement for 190 samples from critically ill patients with differing total protein concentration

In a very similarly designed study of 300 intensive care (ICU) patients, Story *et al* [6] found that mean serum albumin was 26 g/L (range 9-50 g/L). The reference range for albumin is 35-50 g/L so the majority of patients were hypoalbuminemic. Once again there was a linear relationship between patient albumin concentration and difference between "indirect" and "direct" ISE sodium results. As serum albumin decreased, the observed difference between "indirect" and "direct" ISE sodium (I-D) increased. In this study "indirect" ISE sodium measurement resulted in a diagnosis of pseudonormonatremia for 13 % of the 300 patients and pseudohypernatremia for 7 %.

PSEUDOHYPERNATREMIA FAR MORE COMMON THAN PSEUDOHYPONATREMIA

A recent study [7] conducted at a tertiary care hospital in Brisbane, Australia provides the best evidence to date that reduced serum protein and resulting pseudonormonatremia/pseudohyponatremia is a much more frequent problem of "indirect" ISE sodium measurement than increased protein and consequent pseudohyponatremia.

For part of this study the Brisbane researchers recovered all 48,033 serum protein results generated at their hospital laboratory during a 3-month period; this included 2877 results from critically ill patients being cared for in intensive care units (Table II).

	Plasma total protein concentration (g/L)	Number (%) of hospitalized patients	Number (%) of ICU patients
Reduced plasma protein (hypoproteinemia)	<40	256 (0.53)	134 (4.6)
	40-49	1962 (4.1)	714 (24.8)
	50-59	8619 (17.9)	1285 (44.6)
Normal plasma protein (normoproteinemia)	60-69	20329 (42.3)	599 (21.0)
	70-79	14718 (30.6)	135 (4.6)
Increased plasma protein (hyperproteinemia)	80-89	1981(4.1)	10 (0.3)
	90-99	139 (0.3)	0 (0)
	100-109	20 (0.04)	0 (0)
	>110	9 (0.2)	0(0)
TOTAL		48033 (100)	2877 (100)

TABLE II: Total protein concentration of 48,033 hospital patients including 2877 ICU patients

This large database reliably confirms that:

- Increased plasma protein is a rare occurrence among hospital patients, particularly among the critically ill (in this study <5 % of the general hospital population and <0.5 % of those in intensive care were hyperproteinemic)
- Decreased plasma protein is common among hospitalized patients and very common among the critically ill – most (75 % in this study) critically ill patients have reduced plasma protein

In a second part of their study, researchers selected 346 hospitalized patients based on serum protein concentration, the object being to identify three approximately equal-sized groups, each having a different protein concentration range. Group 1 comprised 117 patients with low protein concentration (<60 g/L). Group 2 comprised 105 patients with normal protein concentration (60-83 g/L) and group 3 comprised 124 patients with increased protein concentration (>83 g/L). Blood was sampled from each study patient for sodium measurement by both indirect ISE (I) and direct ISE (D).

Researchers determined that an observed difference (I-D) of 4 mmol/L or greater is significant and represents intermethod disagreement. The difference in sodium values (I-D) for each patient was calculated. As expected, this difference (I-D) was related to protein concentration and ranged from plus 9 mmol/L for those with protein <40g/L to minus 10 mmol/L for those with protein >90 g/L. They determined the proportion of study patients with serum protein in each of nine ranges (< 40 g/L, 40-49 g/L, 50-59 g/L, 60-69 g/L, etc. up to >100 g/L) who had an I-D difference of 4 mmol or more (Table III).

Stratified plasma protein (g/L) of 346 selected patients	Proportion in which difference between direct and indirect ISE sodium was equal to or greater than 4 mmol/L
<40 n=22	0.84
40-49 n=71	0.53
50-59 n=24	0.16
60-69 n=40	0.02
70-79 n=40	0.02
80-89 n=74	0.12
90-99 n=43	0.25
100-109 n=21	0.23
≥110 n=11	0.54

TABLE III: Results of measuring sodium by direct and indirect ISE for 346 selected patients with either hypoproteinemia (<60 g/L), normoproteinemia (60-80 g/L) and hyperproteinemia (>80 g/L).

These determined proportions were then applied to the large database of 48,033 serum protein results to estimate the frequency of significant disagreement between "indirect" and "direct" ISE sodium measurement. This allowed the headline finding of the study, which is that "indirect" ISE overestimates plasma sodium by a clinically significant amount (>4 mmol/L) in around 25 % of samples from the critically ill and around 8 % of samples from all other hospital patients. The data suggests that the discrepancy may approach 10 mmol/L for some samples.

In summary, the results of all four studies [5-8] show that because of their reduced serum protein concentration, critically ill patients are particularly vulnerable to spuriously increased sodium results (pseudonormonatremia, pseudohyponatremia) if indirect ISE methodology is used. The authors of all four studies recommend that for critically ill patients (both adults and neonates) sodium should be estimated using only "direct" ISE techniques. The authors of one of these studies [7] call for the diagnostics industry to standardize sodium measurement across the board so that sodium measurement by "indirect" ISE is no longer available. In such a world, the problematic triad – pseudohyponatremia, pseudonormonatremia and pseudohyponatremia – would be no more than an historic curiosity.

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