Original articles

Effects of Total Plasma Protein Concentration on Plasma Sodium, Potassium and Chloride Measurements by an Indirect Ion Selective Electrode Measuring System

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ABSTRACT

Objective: *Ion selective electrodes (ISE) measure electrolytes by two different technologies, direct and indirect. We wished to investigate the effect of total plasma protein concentration on the plasma sodium, potassium and chloride measurements by indirect ISE compared with measurements by direct ISE.*

Methods: *The evaluation of the objective was performed in a tertiary care hospital on patient blood samples sent to the pathology laboratory for general chemistry analysis. To determine the degree of difference between the two ISE measurements, 195 lithium heparin plasma samples were measured and the results were separated into three groups (65 samples in each group) depending on the protein concentration (e.g. total plasma protein concentration less than, greater than and within the reference range between 62 - 83 g/L). The samples were analysed over a 40 day period on a Hitachi Modular ISE system - indirect ISE (Roche Australia) and Bayer Rapidlab 865 Blood Gas Analyser - direct ISE (Bayer Diagnostics, Australia).*

Results: *Using indirect ISE, low plasma protein concentrations caused a 'pseudohyper' effect in all 3 analytes and a 'pseudohypo' effect with high plasma protein concentrations. The variation in total protein concentration had the greatest effect on plasma sodium measurement. The relationship was non-linear and no accurate predictive value could be calculated for the plasma electrolytes with changes in plasma protein concentrations.*

Conclusions: *The plasma sodium, potassium and chloride measurements are effected by changes in plasma protein concentration when measured by indirect ISE systems. Clinicians must be aware that differences exist between the ISE technologies and in border-line clinical situations, the direct ISE systems provide a more accurate estimate of plasma sodium, potassium, chloride, anion gap, osmolality and strong ion difference calculations, and should be used for clinical decision-making.* (**Critical Care and Resuscitation 2005; 7: 12-15**)

Key words: ion selective electrodes (ISE), direct ISE, indirect ISE, protein effect

Ion selective electrodes (ISE) measure electrolytes by two different technologies. Direct ISE technology measures electrolytes in the plasma component of whole blood, or in other undiluted sample types (e.g. serum,

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plasma or other fluids). This type of technology is used predominately with point-of-care testing (POCT) analysers, traditionally referred to as blood gas analysers. With indirect ISE technology the sample (e.g. plasma, serum or other fluids) is first diluted with diluent of a certain ionic strength before the concentrations of the electrolytes are measured.

Most clinical chemistry laboratory analysers use the indirect ISE technology. With the increased use of POCT, particularly in intensive care units, emergency departments and operating theatres, physicians regularly compare results obtained from POCT with those reported by the laboratory. It is often noted that differences exist between the two sets of results, even with samples collected at the same time. Physicians are often confronted with the problem of which results to use for patient management, particularly when fluid therapy is to be initiated or altered or where there is a need for frequent measurements to guide therapy.

Situations in which this difference in electrolyte estimates may alter clinical practice include the management of traumatic brain injury or profound symptomatic hyponatraemia. During management of severe traumatic brain injury, osmotherapy may be used to limit cerebral oedema and reduce intracranial pressure. Traditionally this was achieved by using agents such as mannitol and then monitoring the measured plasma osmolality. However, as this is time consuming, hypertonic saline has largely replaced mannitol as the agent of choice in many intensive care units,[1] due to the fact that sodium can be measured easily and frequently, with POCT analysers. Sodium is managed in the range of 145 - 155 mmol/L for periods as long as one week, although during this period plasma protein levels can change significantly.

Patients with profound symptomatic hyponatraemia often need correction slowly during which time plasma protein levels can change. Rapid correction of chronic hyponatraemia can cause central pontine myelinolysis, hence accurate measurements are necessary to facilitate the correct rate of sodium rise. Differences in electrolyte concentrations may also have a direct impact on calculated parameters, such as anion gap (AG), calcul-ated osmolality and strong ion difference.[2] The AG differences may lead to difficulties in an accurate determination of acid-base status. This is well supported by Morimatsu *et al*,[6] who report differences in the AG of up to 17.6 ± 6.2 mmol/L in their study between the 2 technologies, which suggests clinicians should use AG results derived from one system rather than switching between 2 systems.

The effect of a high concentration of protein and lipid on sodium measurement by indirect ISE or flame photometry, has been reported previously,[3-6] with both high levels of protein and lipid concentrations resulting in pseudohyponatraemia. Direct ISE technology eliminates this artifact.[3] On the other hand, while low plasma protein concentration produces pseudohypernatraemia,[1] it has been reported only infrequently. In this study we investigated the effect of plasma total protein, albumin, and globulins concentrations on the plasma sodium, potassium and chloride measurement by indirect ISE.

MATERIALS and METHODS

Blood samples with varying protein concentrations were analysed over a 40 day period using both the direct and indirect ISE measurements. Equal numbers, (65) of lithium heparin plasma samples were measured with protein concentrations less than, higher than and within our laboratory's reference range (62 - 83 g/L). Samples were excluded if they were visibly lipaemic. The samples were analysed within 30 minutes of collection.

The plasma electrolytes were measured on Hitachi Modular ISE system (Roche Australia) using indirect ISE technology. The plasma protein and albumin levels were also measured on the Hitachi Modular D or P systems using Biuret and Bromcresol green reagents respectively. The plasma globulins were calculated by the equation: Total Protein - Albumin. Plasma electrolytes were also measured, as was the pH, on the Bayer Rapidlab 865 blood gas analyser (Bayer Diagnostics Australia) using direct ISE techno-logy. The analysers were calibrated as per manufacturers recommendations using manufacturers supplied calibrators.

RESULTS

For each sample, the direct ISE result was subtracted from the indirect ISE result to show the range of difference at the 3 protein levels (table 1). There was a strong but indirect relationship between the change in plasma total protein concentration and difference in electrolyte concentration. Using the Bland Altman approach,[7] the ISE difference was plotted (Y axis) against the plasma protein, albumin, and globulin concentrations (X axis, figure 1). The low plasma protein, albumin and globulins concentrations range lead to a 'pseudohyper' effect in all 3 analytes and the reverse occurred (i.e. a 'pseudohypo' effect) with high concentrations. The variation in total protein, albumin and globulins concentration had the most significant effect on the plasma sodium measurement.

DISCUSSION

The study confirms that variable plasma protein concentrations affect the accuracy of plasma sodium, potassium and chloride measurements when using the

indirect ISE systems. Direct ISE technologies measure electrolyte activity in the water phase only and in whole blood, the cells, proteins and lipids do not influence the analysis. In indirect ISE, a fixed volume of plasma is aspirated and diluted with a diluent for analysis, which means the electrolytes are measured in the volume of total plasma and not the plasma water phase. The plasma sample volume consists of solids (e.g. proteins and lipids) and water (which contains the dissolved electrolytes). In a normal plasma sample, solids represent approximately 7% of the total plasma volume. Indirect ISE systems are standardised to this percentage assuming a 'normal concentration' of solid. When the concentration of the solids in plasma (more often protein than lipids) is changed by > 7% or < 7 %, the ratio of solids to water alters, the water content is decreased or increased causing the observed discrepancies between direct and indirect ISE measurements.

Table 1. The difference range observed between direct and indirect ion selective electrode plasma electrolyte measurements at the three ranges of plasma total protein concentrations

Total protein concentration (g/L)	*Difference range (Indirect ISE - Direct ISE) mmol/L*		
	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)
< 62	0 to 8	-0.2 to 0.4	-6 to 4
63 - 83	-4 to 5	-0.2 to 0.2	-3 to 4
> 83	-7 to 2	-0.5 to 0.1	3 to -9

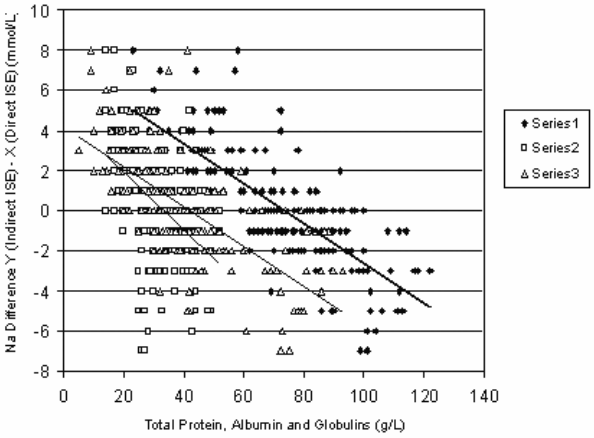

Figure 1. The relationship between the differences of direct minus indirect ion selective electrode resultsfor sodium versus variable total protein concentrations. ♦- total protein, □ - albumin, △-globulins.

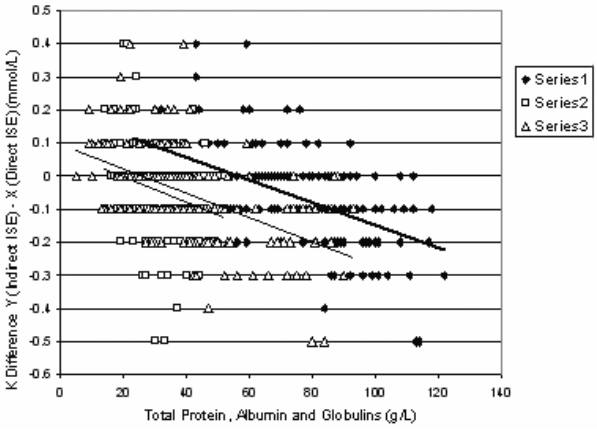

Figure 2. The relationship between the differences of direct minus indirect ion selective electrode resultsfor potassium versus variable total protein concentrations. ♦- total protein, □ - albumin, △-globulins.

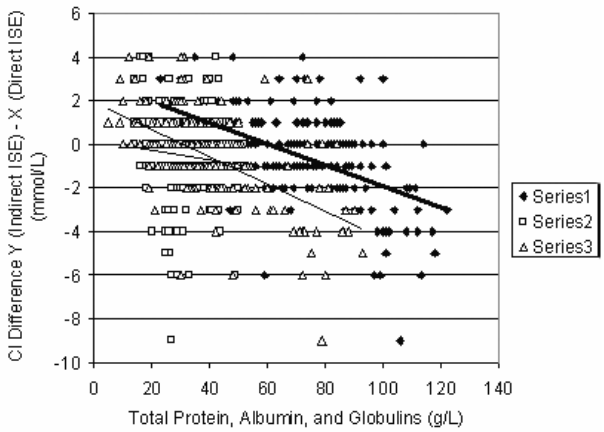

Figure 3. The relationship between the differences of direct minus indirect ion selective electrode resultsfor chloride versus variable total protein concentrations. ♦- total protein, □ - albumin, △-globulins

The non-linear relationship between the total plasma protein concentration and indirect ISE measurements cannot be attributed to any single phenomena. We tested to see if the pH of blood and subsequent charge on proteins may result in differences in binding of sodium, potassium and chloride ions. The correlation coefficients (r^2) of the pH versus ISE differences in all measure-ments were < 0.02, indicating that the pH had no significant effect.

The majority of chemistry laboratory analysers use indirect ISE, because there is lower sample volume requirement and the range of concentration able to be

measured is large and can accommodate other fluid types (e.g. urine). Nevertheless, clinicians need to be aware of the ISE system used to measure the plasma

Table 2. Between-run precision data for analysers

	Bayer Rapidlab 865 Blood Gas Analyser		Hitachi Modular Analyser	
Analyte	*Concentration (mmol/L)*	*CV %*	*Concentration (mmol/L)*	*CV %*
Sodium	113	0.8	127	0.7
	157	0.7	158	0.6
Potassium	3.1	0.7	3.0	1.3
	7.0	0.7	6.0	0.8
Chloride	74	0.9	88	0.8
	121	1.0	120	0.8

electrolytes and the type of effect that a variable protein concentration has when using an indirect ISE analysis. Based on between-run coefficients of variation (CV) for the 3 ISEs as shown in Table 2, differences of up to 3 mmol/L for plasma sodium and chloride and 0.3 mmol/L for plasma potassium can be considered to be due to difference in technical capability between the systems being compared. Unfortunately, the change in electro-lyte concentrations are unpredictable so when dealing with patients who have an abnormal plasma protein concentration, the plasma sample should be analysed by direct ISE for confirmation.

We conclude that the plasma sodium, potassium and chloride are similarly affected in a non-linear manner by changes in plasma protein concentration when measured by indirect ISE systems. In border-line clinical situate-ions, implementing or changing fluid and electrolyte replacement and characterising acid-base status, direct ISE systems provide a more accurate estimate of sodium, potassium and chloride, anion gap, osmolality and strong ion difference calculations, and should be used for clinical decision-making.

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