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Interchangeability of sodium and chloride measurements by indirect and direct ISE assays: Stakeholders, take responsibility!

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To the editors

Electrolytes are among the most commonly requested clinical laboratory tests [1]. There are two methods for measuring electrolytes in plasma, both using the principle of an ion-selective electrode (ISE) [1,2]. The first method, used in point of care blood gas analysers, is direct potentiometry, which measures electrolyte activity in plasma without dilution. The second method, used in routine chemistry analysers in central laboratories, is indirect ISE, which involves a pre-analytical serum or plasma dilution step [1,2]. In the clinical setting, results from both methods are often considered to be interchangeable. Indeed, in theory, all prerequisites are in place to allow interchangeability of test results across both methods, across laboratories, and over time. Both sodium and chloride are well-defined analytes for which an internationally acknowledged JCTLM-listed reference measurement system is available. In addition, commutable reference materials (representative of actual patient samples) are available to structurally evaluate laboratory test performance in external quality assurance (EQA) programs. However, in practice, discrepancies between sodium and chloride results of blood gas analysers and routine chemistry analysers are still an important source of confusion, potentially leading to incorrect diagnosis and treatment of patients. Using anonymised laboratory results of patients admitted to the emergency room and intensive care unit, we here demonstrate in four steps that this lack of interchangeability of sodium and chloride results can be attributed to differences in measurement principle, but also to analytical standardisation issues of the blood gas analysers.

First, we extracted blood gas (RAPIDPoint 500, Siemens Healthcare Diagnostics) and routine chemistry (Modular P800, Roche Diagnostics) sodium and chloride results for patients admitted to the emergency room of our hospital between June 1st 2014 and May 17th 2016. Test results were excluded when the time between blood gas and serum sample analysis exceeded 1 h. In the remaining sample of 1258 patients, mean sodium blood gas results were 2 mmol/L lower than routine chemistry results (step 1 in Table 1, paired samples t-test $p < 0.01$). Mean chloride blood gas results were 3 mmol/L higher than routine chemistry results (step 1 in Table 1, $n = 159$, $p < 0.01$). This was not anticipated, since no systematic differences are expected between sodium results of blood gas analysers and routine chemistry analysers in a random hospital population. The results are displayed graphically in Appendices 1 (sodium) and 2 (chloride).

For sodium and chloride in serum/plasma on routine chemistry analysers, the Dutch EQA organiser SKML has a category 1 trueness verification programme in place with value assigned, commutable EQA-materials covering the clinically relevant concentration range [3]. For blood gas analyser results, a category 1 trueness verification programme is not available in the Netherlands, and comparability of blood gas analyser results is evaluated by national peer group evaluation. Given our almost perfect performance for serum sodium in the EQA programme, we aligned blood gas results with serum results by introducing instrument factors in the blood gas analysers. These were obtained from a selection of the 1258 patients admitted to the emergency room with albumin (Roche Diagnostics, colorimetric method, bromocresol green, reference interval 34–48 g/L) and triglyceride (Roche Diagnostics, colorimetric, GPO-PAP method,

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Table 1
Differences between sodium and chloride measured by blood gas analysis (direct ISE) in lithium-heparin samples and routine chemistry analysis (indirect ISE) in serum, in the original situation, upon alignment of the blood gas analysers and after adjustment for serum albumin.

Step	Description	Emergency Department					Intensive Care Department				
			Blood gas	Serum				Blood gas	Serum		
		Pairs (n)	Mean (SD) (mmol/L)	Mean (SD) (mmol/L)	Mean difference (mmol/L)	P-value	Pairs (n)	Mean (SD) (mmol/L)	Mean (SD) (mmol/L)	Mean difference (mmol/L)	P-value
Sodium											
1	Original situation[a]	1258	137 (5)	139 (5)	-2	<0.01	39	139 (7)	143 (7)	-4	<0.01
2	Upon alignment of blood gas analysers[b]	92	139 (5)	139 (5)	0	0.08	575	140 (5)	142 (6)	-2	<0.01
3	Adjustment of sodium in serum according to Story et al. [4]						575	140 (5)	140 (6)	0	0.16
4	Adjustment of sodium in serum according to local formula[c]						575	140 (5)	140 (6)	0	0.17
Chloride											
1	Original situation[a]	159	101 (6)	98 (7)	+3	<0.01	27	97 (5)	99 (5)	-2	<0.01
2	Upon alignment of blood gas analysers[b]	25	99 (5)	100 (6)	-1	0.06	553	101 (6)	105 (7)	-4	<0.01
3	Adjustment of chloride in serum according to local formula[c]						553	101 (6)	101 (7)	0	0.24

P-values were obtained by paired samples t-test.
[a] Emergency Department: June 1st 2014–May 17th 2016, Intensive Care Department: February 15th 2016–February 23rd 2016.
[b] Emergency Department and Intensive Care Department: December 16th 2016–March 10th 2017.
[c] $Sodium_serum_{adjusted} = sodium_serum_{manufacturer}$ - (5.38-(0.12*albumin)), $chloride_serum_{adjusted} = chloride_serum_{manufacturer}$ - (4.49-(0.01*albumin)).

reference interval 0.80–2.30 mmol/L) concentrations within the reference range (n = 14; equations: $[Na^+]_{aligned} = 0.926 * [Na^+]_{manufacturer} + 12.63$ and $[Cl^-]_{aligned} = 0.905 * [Cl^-]_{manufacturer} + 6.9$). Since the introduction of instrument factors on July 7th 2016, our laboratory technicians compare blood gas results with routine chemistry results every month (with equivalence criteria based on random analytical variation) in order to monitor potential shifts.

As a second step, we investigated the effects of the introduction of the instrument factors in the blood gas analysers, by extracting blood gas and routine chemistry sodium and chloride results (with a maximum time of 1 h between sample analysis) again for patients admitted to the emergency room of our hospital (December 16th 2016 until March 10th 2017). Table 1 (step 2) shows that our approach eliminated the systematic differences between blood gas and serum sodium for these emergency department patients (n = 92, mean difference 0 mmol/L, p = 0.08), and reduced the mean difference in chloride to 1 mmol/L (n = 25, p = 0.06).

It is commonly known that falsely low sodium concentrations might occur in indirect ISE methods in case of hyperlipidemia and/or hyperproteinemia due to the electrolyte exclusion effect (volume displacement effect) [2]. This phenomenon is called pseudohyponatremia. It can be explained by the fixed assumption of a standard composition of serum of 7% non-aqueous and 93% water fractions in indirect ISE methods, which is incorrect in case of hyperproteinemia or hyperlipidemia [1], because the fraction of water is smaller and the absolute amount of sodium is decreased. The dilution introduces an error, causing falsely low sodium results [1]. In case of hypoproteinemia, which is often the case in critically ill patients, the effect is reverse, leading to falsely high sodium concentrations (pseudohypernatremia) [2,4–8]. Since direct ISE methods do not require sample dilution, they are not subject to the electrolyte exclusion effect [2]. As a result, others recommended to preferentially measure electrolytes on blood gas analysers in patients with abnormal protein concentrations [5–8]. However, since blood gas analysers are not available at all clinical wards, we suggest implementation of albumin-corrected sodium and chloride results (a practice which is comparable to the use of albumin-adjusted serum calcium concentrations), as was also recommended by Stove and colleagues [6].

Before alignment of the blood gas analysers in our hospital, a mean difference of 4 mmol/L was observed between sodium measured in parallel blood gas and serum samples from 39 intensive care patients measured by direct ISE and indirect ISE assay, respectively (step 1 in Table 1). For chloride, an average difference of 2 mmol/L was observed (n = 27) for these patients (Table 1, step 1). After alignment of the blood gas analysers in our hospital, we extracted blood gas and routine chemistry sodium and chloride results for intensive care patients (step 2 in Table 1, December 16th 2016 until March 10th 2017, n = 575). The mean difference in sodium results between blood gas and serum for intensive care patients decreased from 4 mmol/L to 2 mmol/L (Table 1, step 2).

As a third step, we applied the formula by Story and colleagues ($sodium_serum_{adjusted} = sodium_serum_{manufacturer}$ - (6.2-(0.16*albumin)) [4] to this dataset to adjust serum sodium concentrations for serum albumin concentrations. We then no longer observed

statistically significant differences between the two methods (Table 1, step 3, $p = 0.16$). This equation can therefore be applied in our hospital when reporting serum sodium results for intensive care patients with hypoalbuminemia (or, less frequently, hyperalbuminemia). Similar results were found when we applied a local formula based on the regression models based on our own dataset (Table 1, step 4). Interestingly, alignment of the blood gas analysers initially increased the differences in chloride results for intensive care patients (Table 1, step 2), showing that the analytical standardisation issues for chloride were previously masked by the opposite effects of the electrolyte exclusion effect. These post-alignment differences disappeared after adjustment of chloride for albumin in serum (Table 1, step 3).

This practical example illustrates that standardisation of sodium and chloride across methods and matrices is not a simple task and emphasises the need for a close collaboration between laboratory specialists and clinicians regarding education on (pitfalls in) laboratory medicine. Standardisation requires extensive knowledge of measurement principles and correct implementation of the metrological traceability concept by laboratory specialists, EQA organisers and manufacturers. All stakeholders should take responsibility to improve standardisation and interchangeability of sodium and chloride results in blood gas and serum/plasma to prevent potential patient harm [9].

Author contributions

•WPJ den Elzen: This author was responsible for conception and design of the study, acquisition of data, data analysis, interpretation of results, drafting of the manuscript, and final approval of the manuscript.

•CM Cobbaert: This author was responsible for conception and design of the study, interpretation of results, revising the article for intellectual content, and final approval of the manuscript.

•MS Arbous: This author was responsible for interpretation of results, revising the article for intellectual content, and final approval of the manuscript.

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•E de Jonge: This author was responsible for interpretation of results, revising the article for intellectual content, and final approval of the manuscript.

•PW Schenk: This author was responsible for conception and design of the study, acquisition of data, data analysis, interpretation of results, drafting of the manuscript, and final approval of the manuscript.

Conflicts of interests/financial disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2019.e00126.

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