Comparison of Point-of-Care Versus Central Laboratory Measurement of Electrolyte Concentrations on Calculations of the Anion Gap and the Strong Ion Difference

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Background: Clinicians calculate the anion gap (AG) and the strong ion difference (SID) to make acid–base diagnoses. The technology used is assumed to have limited impact. The authors hypothesized that different measurement technologies markedly affect AG and SID values.

Methods: SID and AG were calculated using values from the point-of-care blood gas and electrolyte analyzer and the central hospital laboratory automated blood biochemistry analyzer. Simultaneously measured plasma sodium, potassium, and chloride concentrations were also compared.

Results: Mean values for central laboratory and point-of-care plasma sodium concentration were significantly different (140.4 ± 5.6 mEq/l vs. 138.3 ± 5.9 mEq/l, P < 0.0001), as were those for plasma chloride concentration (103.4 ± 6.0 mEq/l vs. 105.4 ± 6.0 mEq/l, P < 0.0001) but not potassium. Mean AG values calculated with the two different measurement techniques differed significantly (17.6 ± 6.2 mEq/l for central laboratory vs. 14.5 ± 6.0 mEq/l for point-of-care blood gas analyzer, P < 0.0001). Using the Stewart–Figge methodology, SID values also differed significantly (43.7 ± 4.8 mEq/l vs. 40.7 ± 5.6 mEq/l, P < 0.0001), with a mean difference of 3.1 mEq/l (95% limits of agreement, −3.4, 9.5 mEq/l). For 83 patients (27.6%), differences in AG values were as high as 5 mEq/l or more, and for 46% of patients whose AG value was outside the reference range with one technology, a value within normal limits was recorded with the other.

Conclusions: Results with two different measurement technologies differed significantly for plasma sodium and chloride concentrations. These differences significantly affected the calculated AG and SID values and might lead clinicians to different assessments of acid–base and electrolyte status.

CRITICALLY ill patients undergo frequent measurements of blood electrolytes. From electrolyte measurements, clinicians frequently calculate the anion gap (AG) and the strong ion difference (SID) to assist them in characterizing acid-base status and to guide clinical decision-making. Sometimes these results are essential for medical decisions. Some reports suggest that the availability of a bedside electrolyte-measurement method (so-called point-of-care testing) might have beneficial effects on patient care.1,2 In particular, measurements of arterial blood gases, blood glucose and potassium, hemoglobin, and hematocrit are most likely to be of benefit in bedside monitoring.3 Machines are now available either in the intensive care unit (ICU) or very close to it to perform such measurements. A recent study, however, shows that there might be differences between measurements with point-of-care technology and central laboratory facilities.4

The Stewart–Figge methodology5,6 has been increasingly used in several areas of medicine7–15 to help clinicians understand changes in acid–base balance. However, both the Stewart–Figge calculations and the AG calculations depend on measurements of electrolyte concentrations, and errors in individual measurements can have a compounding effect when used as part of such calculations. Thus, the bias and imprecision of two different measurement technologies might significantly affect the accuracy, reproducibility, and clinical utility of this approach.

Accordingly, we studied 300 simultaneous paired blood samples from critically ill patients and compared the values obtained with point-of-care technology and those obtained with standard central laboratory technology in our hospital. We compared the two different methods for determining plasma sodium, potassium, and chloride concentrations and the AG and SID values.

Materials and Methods

Clinical Study

The data collection for this study was classified as an anonymous and confidential quality audit for which the institutional ethics committee waives the need for informed consent.

We retrospectively examined data from 300 consecutive critically ill patients admitted to our ICU for at least 24 h, from May 2000 until March 2001. The data needed for analysis were collected from the ICU staff as part of standard patient care and were electronically stored and available for computer-based retrieval. All biochemical information was routinely obtained by testing arterial blood after insertion of an arterial catheter on admission to the ICU. Thus, from such records, we retrospectively obtained biochemical data and demographic information, such as age, sex, and Acute Physiology and Chronic Health Evaluation (APACHE) II score.16 No additional sampling was required.

Arterial blood samples were collected in heparinized
blood-gas syringes (Rapidlyte; Chiron Diagnostics, East Walpole, MA) and analyzed in the point-of-care blood gas and electrolyte analyzer (Bayer Diagnostics Rapilab 865; Bayer Australia, Sydney, Australia). The analyzer measured ions at 37°C. It obtained an aliquot of heparinized whole blood from the syringe for subsequent measurement. Sodium was measured with use of an ion-selective electrode with silver-silver chloride wire surrounded by an electrolyte solution. This solution is separated from the sample by a membrane. The membrane is a specially formulated glass capillary that is highly selective for sodium ions over other clinically encountered cations.

Potassium was measured with use of an ion-selective electrode with silver-silver chloride wire surrounded by an electrolyte solution and with a membrane that consisted of the ionophore valinomycin immobilized in a plasticized polyvinyl chloride matrix. Chloride was measured with use of silver-silver chloride wire surrounded by an electrolyte solution with a membrane of a derivatized quaternary ammonium compound that is immobilized in a polymer matrix. This membrane acts as an ion exchanger with a high selectivity for chloride ions over other ions present in the sample (Bayer Diagnostics Rapilab 865).

Nursing staff from the ICU, who had been trained in the use of the machine by support technical staff, performed point-of-care analysis. Samples were not stored on ice but were analyzed immediately after collection. We collected data from the machine output: sodium, potassium, chloride, lactate, ionized calcium, arterial pH, and PaCO2 values.

For each data set, paired samples were simultaneously drawn with use of a vacuum technique with lithium-heparin tubes with gel separation (Vacuette; Greiner Laborteknik, Kremsmunster, Austria). Samples were centrifuged at 4,200 rpm for 10 min to separate plasma from cells. The samples were analyzed by clinical staff at the hospital central laboratory by means of a Hitachi multichannel biochemical analyzer (Hitachi 747; Roche Diagnostics, Sydney, New South Wales, Australia) for the measurement of multiple biochemical variables such as plasma sodium, chloride, potassium, and total magnesium concentrations, which were used for analysis. Sodium was measured with an ion-selective electrode with a polyvinyl chloride membrane containing a neutral carrier, which provides a cavity for the capture of the sodium ion. Potassium was also measured with use of an ion-sensitive electrode with a polyvinyl chloride membrane, but the membrane was modified with the antibiotic valinomycin, which makes the electrode selective for the potassium ion.

Finally, chloride was measured with use of an ion-selective electrode membrane with an ion exchanger, which pairs with chloride ions (Hitachi 747). Samples were processed within 2 h of being drawn and not stored on ice. All data were stored in computerized records. All data were retrieved from these records for analysis. We then compared these results with regard to plasma sodium, potassium, and chloride concentrations.

### Experimental Studies

To explore possible explanations for our findings, we conducted two simple experimental studies.

First, we sought to test for the possible electrolyte-diluting effect of heparin in the point-of-care syringe. Thus, we compared electrolyte measurements with the point-of-care blood gas analyzer, using different amounts of blood in the syringe. Blood from a healthy volunteer (one of the authors) was drawn into nine syringes, each containing 1 ml blood, and nine other syringes, each containing 3 ml of blood. The syringes were put on ice until measurement. We measured sodium, potassium, ionized calcium, and chloride concentrations in the syringe specimens in random order.

Second, we sought to test whether the use of whole blood as the source of sampling might be responsible for some of our findings. Thus, we collected plasma samples from patients after central laboratory measurement, placed these plasma samples in nonheparinized syringes, and put the syringes into the point-of-care blood gas analyzer. We then measured sodium, potassium, ionized calcium, and chloride concentrations directly from plasma.

### Strong Ion Difference

Quantitative physical–chemical analysis was performed with use of Stewart’s quantitative biophysical methods, modified by Figge et al. This method involves calculating the SID as follows (all concentrations in mEq/l):

\[
\text{SID} = [\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] - [\text{Cl}^-] - \text{lactate}
\]

We calculated the SID on the basis of plasma sodium, potassium, and chloride concentrations determined by the two different technologies.

We used the values for ionized calcium and lactate obtained from a single technology (point of care) because they were not measured by the central laboratory. Similarly, we used the value for total magnesium as routinely determined by the central laboratory, because total magnesium is not routinely measured with point-of-care technology.

The SID equation does not take into account the role of weak acids (CO2, albumin, phosphate) in the balance of electrical charges in plasma water; thus, it is best called SID apparent (SIDa), and it will be referred to as such in the manuscript. This is expressed through the...
calculation of the SID effective (SIDe). The formula for SIDe, as determined by Figge et al.,\textsuperscript{6} is as follows:

\[
\text{SIDe} = \frac{1.000 \times 2.46 \times 10^{-11} \times \text{PCO}_2/(10^{-\text{pH}}) + [\text{Alb}]}{\text{H11001}} \times (0.123 \times \text{pH}^{-0.631}) + [\text{Phos}] \times (0.309 \times \text{pH}^{-0.469})
\]

where PCO\textsubscript{2} is in mm Hg, albumin (Alb) in g/l, and phosphate (Phos) in mM.

This formula quantitatively accounts for the contribution of weak acids to the electrical charge equilibrium in plasma. Once weak acids are quantitatively taken into account, the SIDa − SIDe theoretically should equal 0 (electrical charge neutrality). If this is not so, there must be unmeasured charges to explain this ion gap, which is called the SIG, as previously described:\textsuperscript{9}

\[
\text{SIG} = \text{SIDa} - \text{SIDe}
\]

A positive value for SIG must represent unmeasured anions (such as keto acids, urate, sulfate, citrate, pyruvate, acetate, gluconate) that theoretically should be present in the blood to account for the measured pH, the measured levels of strong and weak ions, and the need to maintain isoelectricity.

From the above observations, it is clear that an accurate analysis based on Stewart-Figge methodology requires an accurate SIDa calculation and that the value of the SIG depends heavily on that of the SIDa.

The traditional AG was also calculated as \( \text{AG} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] - [\text{HCO}_3^-] \), with a normal reference range of 12–20 mM at our central laboratory with use of the Hitachi 747 multichannel biochemical analyzer as described in the Methods section.

Statistical Analysis
All statistical analysis was performed with use of a commercially available statistical program, Statview (Abacus, Berkeley, CA). For data analysis we used the paired \( t \) test. The Wilcoxon rank sum test or Mann-Whitney test was used for the analysis of experimental studies. Data are presented as means with SD or medians with interquartile range. Agreement between the two analyzers was assessed using the Bland-Altman approach.\textsuperscript{17} A \( P \) value of less than 0.05 was considered statistically significant.

Results
Our 300 patients had a mean age of 60.2 ± 18.2 yr and a mean APACHE II score of 17.9 ± 6.8. The 300 pairs of samples were from 174 males (58%) and 126 females (42%). Mean values were as follows: arterial pH, 7.37 ± 0.10 (range, 6.93–7.61); PaCO\textsubscript{2}, 43.5 ± 12.3 mm Hg (11.0–97.0); base excess, −0.6 ± 7.0 mEq/l (−24.8–23.4); ionized calcium, 1.17 ± 0.11 mM (0.84–1.52); magnesium, 0.84 ± 0.25 mM (0.36–2.27); and lactate, 2.53 ± 2.33 mM (0.10–18.83).

The mean plasma sodium concentration was 140.4 ± 5.6 mM with central laboratory testing vs. 138.3 ± 5.9 mM with point-of-care testing (\( P < 0.0001 \)). The mean difference in plasma sodium concentration was 2.1 mM (95% limits of agreement: −0.62, 3.82 mM) (fig. 1). The mean plasma potassium concentration was 4.20 ± 0.80 mM vs. 4.21 ± 0.74 mM (\( P = 0.51 \)), and the mean difference in plasma potassium concentration was −0.15 mM (95% limits of agreement: −0.82, 0.79 mM). The mean plasma chloride concentration was 102.4 ± 6.5 mM vs. 103.4 ± 6.0 mM (\( P < 0.0001 \)), and the mean
difference in plasma chloride concentration was $-1.0 \text{ mmol/L}$ (95% limits of agreement: $-6.6, 4.6 \text{ mmol/L}$) (fig. 2). Consequently, the calculated AG from the two different measurement techniques differed significantly ($17.6 \pm 6.2 \text{ mEq/L}$ for central laboratory measurements vs. $14.5 \pm 6.0 \text{ mEq/L}$ for point-of-care measurements; $P < 0.0001$). Furthermore, the mean difference for the calculated AG was $3.1 \text{ mEq/L}$ (95% limits of agreement: $-3.4, 9.5 \text{ mEq/L}$) (fig. 3). The SIDa values were significantly different when values from the two biochemical blood analyzers were used. The mean SIDa for point-of-care measurements was $40.7 \pm 5.6 \text{ mEq/L}$, compared with $43.7 \pm 4.8 \text{ mEq/L}$ for central laboratory measurements ($P < 0.0001$). Of course, the mean difference in the calculated SIDa was the same as for the AG (fig. 4).

Among the 300 patients, 78 had an abnormally high AG determined by central laboratory technology. Of these 78 patients, however, only 36 (46%) had abnormally high AG values determined in point-of-care measurements ($P < 0.0001$). Of the remaining 222 patients with a normal AG determined by central laboratory technology, 4 had an elevated AG with point-of-care technology ($P < 0.0001$) (table 1). For 83 patients the difference in AG between the two technologies was $>5 \text{ mEq/L}$, for 33 patients it was $>7 \text{ mEq/L}$, and for 5 patients it was $>10 \text{ mEq/L}$.

Details on agreement of measurements with the two
technologies are presented in table 2. Even in the normal range of arterial pH, PaCO₂, and base excess, there were substantial differences in AG measurements between the two technologies.

Furthermore, many patients classified as having a normal sodium, chloride, or AG value with one technology had an abnormal value with the other (table 1).

In our experimental studies directed at understanding possible explanations for our findings, we observed that the median sodium and calcium concentrations were significantly lower when small amounts of blood (1 ml instead of 3 ml) were drawn into the heparinized blood gas syringe (table 3). We also observed that when plasma instead of whole blood was the sample source for the point-of-care blood gas analyzer, the sodium, calcium, and chloride concentrations remained significantly different from those determined by the central laboratory (table 3).

### Discussion

Our study shows significant differences in the sodium and chloride concentrations when a point-of-care blood gas analyzer is used compared to central laboratory measurements. Table 1 provides a summary of the prevalence of abnormal values for sodium, chloride, and anion gap.

Table 1. Prevalence of Abnormal Values of Sodium, Chloride, and Anion Gap

<table>
<thead>
<tr>
<th></th>
<th>Laboratory</th>
<th>+</th>
<th>-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatremia</td>
<td></td>
<td></td>
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<tr>
<td>Point-of-care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>27</td>
<td>263</td>
<td>290</td>
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</tr>
<tr>
<td>Total</td>
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<td>300</td>
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<tr>
<td>Hyponatremia</td>
<td></td>
<td></td>
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<tr>
<td>Point-of-care</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>+</td>
<td>31</td>
<td>39</td>
<td>70</td>
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<tr>
<td>-</td>
<td>2</td>
<td>228</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>267</td>
<td>300</td>
<td></td>
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<tr>
<td>Hyperchloremia</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Point-of-care</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>+</td>
<td>49</td>
<td>37</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>10</td>
<td>204</td>
<td>214</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>241</td>
<td>300</td>
<td></td>
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<tr>
<td>Hypochloremia</td>
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<tr>
<td>Point-of-care</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>29</td>
<td>15</td>
<td>44</td>
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<tr>
<td>-</td>
<td>4</td>
<td>252</td>
<td>256</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>267</td>
<td>300</td>
<td></td>
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<tr>
<td>High AG</td>
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<tr>
<td>Point-of-care</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>36</td>
<td>4</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>42</td>
<td>218</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>222</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>High AG (BE&lt;5)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Point-of-care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>24</td>
<td>18</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>18</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

| Reference ranges for central laboratory measurement: sodium 135–145, chloride 95–107, AG 12–20 mEq/l. |

AG = anion gap; BE = base excess.

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![Diagram showing the mean difference in strong ion difference apparent (SIDa) with the two methods (n = 300).](image-url)
gas and electrolyte analyzer was compared with a central laboratory automated biochemical analyzer. These differences in measurement significantly affect the conventional AG value (with extreme variations of up to 15 mEq/l), the calculated SIDa value (with similar extremes of variation), and individual electrolyte values (sodium and chloride). These wide variations in the values of electrolytes and fundamental acid-base variables are clinically relevant and require detailed discussion.

**Magnitude of Differences**

Generally, for sodium, potassium, and chloride concentrations, the mean differences between two technologies were small (2.1 mm, -0.15 mm, and -1.0 mm, respectively). However, the 95% limits of agreement of these differences reached -2.6 and 6.8 mm, -0.82 and 0.79 mm, and -6.6 and 4.6 mm, respectively. These wide limits of agreement can therefore lead to marked differences in individual patients and can have a compounding effect on the AG and SIDa (95% limits of agreement: -3.4, 9.5 mEq/l). The SIDa is used to calculate the strong ion gap (a quantitative measure of unmeasured anions). Thus, any mEq/l change in SID will translate into an equal change in the value of the SIG. Given that many different laboratory technologies are applied to such calculations, it is not surprising to find wide differences in the reported SIG value. Such values have varied from close to zero to 3 mEq/l, 8 mEq/l, or even 11 mEq/l, causing investigators to come to different conclusions about the prognostic significance of the SIG.

The same effect of these changes applies to the conventional AG. For example, among 78 patients who had an abnormally high AG determined by central laboratory measurements, more than 50% of patients had a normal AG value determined by point-of-care measurements. One patient had an AG of 22.4 mEq/l determined in central laboratory measurement but an AG of 12.2 mEq/l in point-of-care measurements. Such a difference could easily lead clinicians to different interpretations of acid-base status. It represents another gap in the AG and, of course, in the SIG.

Furthermore, one could consider only those patients with evidence of metabolic acidosis (base excess, < -5 mEq/l; table 2). Close to 50% of these patients had a high AG with one technique but a normal AG with the other.

**Possible Explanations**

There are several potential explanations for these differences in measurement. First, the difference in the elapsed time between sampling and analysis for the point-of-care measurement and the central laboratory measurement might have influenced the electrolyte concentrations in plasma. However, this difference is most likely to affect potassium levels, which was not the case in our study.

Second, sample preparations were different. Different syringes or tubes, which include anticoagulants for sample preparation, might account for differences in electrolyte concentrations. However, both tubes contained heparin in solid phase. Nonetheless, the proportional volume of the heparin in the blood gas syringe was greater and might have led to calculation of a lower sodium concentration. Our experimental observations with use of different volumes of blood in the point-of-care syringes suggest this might be true. Indeed, others have made similar observations.

Finally, whole blood is inserted in the sampling port of the blood gas analyzer, whereas with standard multichannel technology, plasma is obtained for analysis by centrifugation. This difference might affect the concentration of electrolytes. However, even when we inserted plasma obtained by centrifugation directly into the point-of-care blood gas analyzer, we found a lower sodium concentration and a higher chloride concentration, as had been the case with whole blood. This observation suggests that actual differences in electrode activity might have been responsible, in part, for our findings.

Because we measured electrolytes with only two machines, the results could reflect a bias or imprecision of one or both analyzers in comparison with accepted standards of laboratory performance. This is unlikely, because we measured 300 samples over a period of 10 months and the analyzers were checked daily (quality control) and also regularly inspected and tested for accreditation, in accordance with Australian laboratory standards of laboratory performance. This is unlikely, because we measured 300 samples over a period of 10 months and the analyzers were checked daily (quality control) and also regularly inspected and tested for accreditation, in accordance with Australian laboratory standards of laboratory performance.

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**Table 3. Results of Experimental Studies**

<table>
<thead>
<tr>
<th></th>
<th>1 ml</th>
<th>Interquartile Range</th>
<th>3 ml</th>
<th>Interquartile Range</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume effect</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>140.1</td>
<td>140.1–143.3</td>
<td>143.3</td>
<td>142.0–143.5</td>
<td>0.0009</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.34</td>
<td>4.28–4.41</td>
<td>4.32</td>
<td>4.27–4.38</td>
<td>0.57</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>1.23</td>
<td>1.23–1.24</td>
<td>1.28</td>
<td>1.27–1.28</td>
<td>0.0011</td>
</tr>
<tr>
<td>Chloride</td>
<td>102</td>
<td>102.0–103.0</td>
<td>102</td>
<td>102.0–103.0</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Plasma measured</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>138.0*</td>
<td>136.5–141.0</td>
<td>135.8†</td>
<td>134.6–139.3</td>
<td>0.0077</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.10*</td>
<td>3.69–4.53</td>
<td>4.09†</td>
<td>3.79–4.58</td>
<td>0.29</td>
</tr>
<tr>
<td>Chloride</td>
<td>100.0*</td>
<td>96.8–104.0</td>
<td>104.0†</td>
<td>101.3–107.3</td>
<td>0.0077</td>
</tr>
</tbody>
</table>

* Measured with central laboratory technology. † Measured with point-of-care technology.
standards. Both analyzers performed in accordance with the standards for the measurement of each analyte under study.

Furthermore, previous studies with two similar blood gas analyzers by different manufacturers yielded results similar to ours for serum sodium and potassium.4

What Are the Correct Values?

It is not possible to determine a correct value for the variables under measurement or to establish whether the central laboratory or point-of-care value was closer to the true value for each analyte. Laboratory performance is tested not in absolute terms but in relative terms. For these reasons, simple alterations in the reference range is tested not in absolute terms but in relative terms. For these reasons, simple alterations in the reference range are not justifiable or useful. The external quality assurance methodology compares a given laboratory to a large cohort of other national laboratories. The test applied is one of variance from the mean of all laboratories for single batches of plasma. The two laboratories in this study performed in the top quartile. Such performance does not, however, tell the investigator whether the true value for chloride is 102 or 104 mm.

The ability of technology to provide a true value could be tested only if a chloride-free sample of blood were spiked with a known, accurately measured quantity of chloride. This is impossible. These issues extend from the measurement of a single electrolyte to the assessment of derived variables such as the SIDa and the SIG. In particular, it is not surprising that so much variation is found in the value assigned to the SIG, given that nine variables are used for its calculation, each one with its SD and potential measurement error and bias. On the basis of the normal reference mean values from our central laboratory, the mean SIG can be calculated as 7.6 mEq/l. On the basis of the means of normal reference laboratory values provided in the 14th edition of Harrison’s Textbook of Medicine, its value is 6.5.22

This value should represent the balance between unmeasured anions and unmeasured cations. With use of the Ciba Geigy scientific tables for the components of human blood23 and other published work,24 many unmeasured cations can be identified (zinc, copper, aluminum, selenium, iron, manganese, cadmium, chromium, molybdenum), but these add up to no more than 0.1 mEq/l. Thus, if published laboratory values are correct, there should be somewhere between 6.5 and 7.5 mEq/l of unmeasured anions in plasma. Many such unmeasured anions can be identified (urate, ketones, ascorbate, sulfate, several fatty acids, pyruvate, aspartate, glutamate, bromide, iodide, fluoride, nitrate, guanidinoacetate, succinate, glycolate, oxalate, nicotinate, pantothenate, thiocyanate, folate, and citrate) with use of information from scientific tables.25 However, also on the basis of such information, their total value in mEq/l would appear to be between 2.5 and 4.5 mEq/l, according to diet, metabolic state, gender, and age.23 Clearly, this area of medicine requires further detailed investigation.

Do Differences in Laboratory Values for Sodium and Chloride Matter?

The clinical impact of differing evaluations of the patient’s acid–base status is unknown. Investigations or therapeutic interventions might be implemented in response to an AG that is >7 mEq/l higher than initially believed, as was the case for more than 10% of patients. These interventions might include further investigations to diagnose the source of unmeasured anions such as the measurement of lactate or ketone bodies. If the base excess were negative, the anion gap normal, and the chloride increased, an alteration in the choice of intravenous fluids might occur (avoidance of normal saline). If the sodium were abnormally elevated with one machine but not the other (as for nearly 10% of our patients), changes in the amount and speed of administration of water (nasogastric water or 5% dextrose) might be prescribed. Such changes might apply in the opposite direction if the sodium were low (close to 13% of cases). If the chloride were high with one machine but not the other (close to 15% of cases), loop diuretics might be prescribed to excrete the excess chloride or intravenous fluids rich in chloride (saline) might be withheld. Perhaps investigations of tubular function might take place. These observations would apply in the opposite direction for hypochloremia (close to 6% of cases).

These interventions are unpredictable, relate to clinicians’ preferences, and should vary greatly in magnitude but are nonetheless easily conceivable. Their consequences in terms of outcome could be determined only by a double-blind controlled trial in which patients were randomized to either point-of-care or central laboratory-based testing to guide subsequent care.

Limitations

Our study has several limitations. First, it investigated the SIDa and AG in a large sample of critically ill patients from a single tertiary unit. Its findings might not apply to other populations. However, the ICU in question admits a variety of surgical and medical patients, and its population is likely to be representative of other general ICU populations. The scatter of values for the acid–base variables under investigation supports this contention. Second, this study compared the AG and SIDa values obtained with only two technologies. A third technology would have been desirable to provide further information on variance and accuracy. However, these are the only two technologies available in our institution, and the additional analyses would have been costly and logistically very difficult. In addition, the samples would have had to be sent to another institution, and there would have been a significant delay before measure-
ments were done, thus adding uncertainty about the findings.

Furthermore, the two technologies under scrutiny are used by hundreds of laboratories in Western countries, making our observations highly relevant to medical practice in many institutions. According to the manufacturers, over 7,000 point-of-care machines just like ours are currently in use all over the world, and 150 multichannel Hitachi analyzers of the type used in our hospital are currently in use in central laboratories worldwide. Thus, we believe that the principles established by our observations are likely to be generalizable.

In conclusion, our study shows that the agreement of plasma sodium and chloride concentrations determined by two commonly used different technologies is limited. These differences significantly affect the SIDa calculated with the Stewart–Figge methodology and consequently the SIG measurements, as well as the conventional AG and major electrolyte assessments. They could lead clinicians to significantly different interpretations of a patient’s electrolyte and acid–base status. As more and more point-of-care measurements are being applied to the care of the critically ill, physicians need to be aware of these differences. They also need to be aware of issues such as imprecision, bias, and lack of a gold standard for accuracy in the measurements of all analytes used for acid–base assessment, if they wish to avoid potential misdiagnoses and unnecessary treatments or investigations.

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References