Falsely Increased i-STAT Chloride Results for Blood Samples with Increased Urea, J. Keith Pinckard,1 Janet Zahn,2 Lori Ashby,2 Curtis A. Parvin,1 and Mitchell G. Scott1*
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Decentralized testing is becoming more common as technology lends itself to the development of accurate point-of-care testing devices. The i-STAT® System (Abbott) is used at our institution in two same-day outpatient surgery centers to measure electrolytes, urea nitrogen, glucose, and hematocrit in whole blood by use of the “6+ cartridge”. Our quality assurance program compares results from the i-STAT to those from the central laboratory on a weekly basis. Central laboratory values for sodium, potassium, chloride, glucose, and urea are obtained from plasma of the same heparin-anticoagulated patient sample collected before surgery.

After implementing the i-STAT at the second outpatient surgery center (October 2000), we observed an unusually high frequency of i-STAT chloride concentrations that were $\geq 6$ mmol/L higher than results from the Dimension RxL (Dade Behring) in the central laboratory. This phenomenon occurred with all five i-STAT devices that are rotated through both decentralized testing areas. Samples from 176 patients were compared from October 2000 through mid-April 2001. Although all of the other analytes showed good agreement between the i-STAT and the central laboratory, 59 of the 176 samples (34%) produced chloride values on the i-STAT that were $\geq 6$ mmol/L higher than the RxL values. i-STAT chloride values were $\geq 8$ mmol/L higher than the laboratory values for 31 samples and $\geq 10$ mmol/L higher for 10. This exceeded our acceptability standards for intermethod agreement and prompted investigation.

All quality-control values were acceptable during this time, and our decentralized testing staff could identify no operator errors. All patients with a chloride $\geq 6$ mmol/L higher by the i-STAT method also had an abnormally high urea nitrogen [reference interval, 2.9–8.9 mmol/L (80–250 mg/L)]. The magnitude of the increased chloride values from the i-STAT increased in a roughly linear fashion with increasing urea concentrations (Fig. 1A). Of 176 samples tested during this period, 102 (58%) were from patients with renal failure undergoing either peritoneal dialysis or hemodialysis. Samples from these dialysis patients accounted for 54 of the 58 (93%) samples with i-STAT chloride values $\geq 6$ mmol/L higher than the central laboratory result (Table 1). In all patients with a urea nitrogen $\geq 8.9$ mmol/L (250 mg/L), the mean i-STAT chloride values averaged 5.8 mmol/L higher than the mean of the RxL results, whereas in patients with a urea nitrogen $\leq 8.9$ mmol/L (250 mg/L), the mean i-STAT values were only 1.3 mmol/L higher than the mean of the central laboratory’s result (Table 1). The same trend occurred in the subset of 102 patients on dialysis, where the i-STAT chloride averaged 6.1 mmol/L higher than the RxL result in patients with urea $> 8.9$ mmol/L (250 mg/L), but only 2.6 mmol/L higher in patients with urea $\leq 8.9$ mmol/L (250 mg/L). Only one patient with a normal urea [7.9 mmol/L (220 mg/L)] had an unacceptably higher i-STAT chloride value (6 mmol/L greater than the RxL result), but even this patient was on dialysis.

These renal disease patients were all having procedures for creation or revision of arteriovenous fistulas in the same outpatient surgery center. Implementation of the i-STAT device at this surgery center coincided with the onset of frequent errors for chloride. No samples from the other outpatient surgery center where the i-STAT had been in use for 6 years produced i-STAT chloride values with these large discrepancies. To investigate whether these discrepancies represented an interference in the i-STAT chloride method rather than the RxL method, we...
obtained six random samples from the laboratory with urea nitrogen between 15.4 and 664 mmol/L and five samples with urea nitrogen < 8.9 mmol/L (250 mg/L) and compared the i-STAT values to those obtained by a Hitachi 747 (Roche) analyzer. The i-STAT chloride values averaged 6.8 mmol/L higher than the Hitachi values for the samples with increased urea and only 1.2 mmol/L higher for the samples with normal urea.

To assess whether an increased urea is sufficient to falsely increase chloride results from the i-STAT System, we added urea (SigmaUltra; > 99.9% purity, containing < 0.05% chloride; Sigma Chemicals) to heparinized whole blood with a normal urea concentration [4.3 mmol/L (120 mg/L)]. The i-STAT chloride increased in a linear fashion ($R^2 = 0.91$) with increasing concentrations of added urea (Fig. 1B). The samples were then centrifuged, and the plasma was assayed for chloride by the RxL, which gave constant chloride values regardless of the urea concentration.

In summary, routine method comparisons showed an association between high urea and increased chloride results from the i-STAT System, and addition of urea to whole blood replicated this interference. However, not all patients with increased urea showed this interference. In fact, only 58 of the 103 patients (56%) with a urea values. Like the earlier studies, our previous study included a very small number of renal failure patients: only 14 of 369 samples had urea nitrogen values > 179 mmol/L (500 mg/L) (5).

To our knowledge, only one group has compared i-STAT values with central laboratory values in a group of dialysis patients (6). When chloride values from 28 dialysis patient samples were compared with the Beckman CX7 values, a mean difference of only 1.8 mmol/L was found, but the urea concentration appeared to be within the reference interval in more than one-half of these samples. Of particular note was that the i-STAT chloride values were 5.8 mmol/L higher than the laboratory value when nine dialysate samples were compared. In most of these previous comparisons, including our own, the occasional increased chloride values from the i-STAT have been dismissed as not being clinically significant. However, none of these studies examined a large number of patients with chronic renal failure and increased urea.

Because patients with chronic renal failure are prone to acidosis, we believe that differences in chloride values as large as we observed here are medically significant. One

### Table 1. Differences in i-STAT and central laboratory chloride values (mmol/L) in patients with normal and increased plasma urea.

<table>
<thead>
<tr>
<th>Urea nitrogen</th>
<th>≤ 8.9 mmol/L (250 mg/L)</th>
<th>&gt; 8.9 mmol/L (250 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Number of patients</td>
</tr>
<tr>
<td>Patient group</td>
<td>$\Delta Cl^{a} &lt; 6$</td>
<td>$\Delta Cl \geq 6$</td>
</tr>
<tr>
<td>All</td>
<td>72</td>
<td>1</td>
</tr>
<tr>
<td>Dialysis</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Nondialysis</td>
<td>62</td>
<td>0</td>
</tr>
</tbody>
</table>

$^{a} \Delta Cl$ (mmol/L) is defined as i-STAT $[Cl^{-}]$ − RxL $[Cl^{-}]$. 

We believe that the interference in chloride measurements may have been present since the introduction of the i-STAT. In the first report describing the performance of the i-STAT, 7 of 143 i-STAT chloride values were $\geq 6$ mmol/L higher than Kodak Ektachem values, but we could not determine the corresponding urea values (2). Others examining the i-STAT did not report significant differences between the i-STAT and either the Kodak Ektachem (3) or the Beckman CX7 (4), but they did report that chloride values had the lowest $r$ and highest $S_{yx}$ values among the tests on the i-STAT. Scatter plots from these studies show some samples with i-STAT chloride values $\geq 6$ mmol/L higher than the comparison method, but it is not possible from the published reports to associate these with corresponding urea concentrations, of which very few were increased (3, 4).

When we evaluated the i-STAT in an emergency department setting, we found that 11 of 379 chloride values differed by $\geq 6$ mmol/L compared with the Kodak Ektachem, but only 2 of these were higher than the Ektachem value (5). Interestingly, retrospective review of our data showed that these two samples had increased urea values. Like the earlier studies, our previous study included a very small number of renal failure patients: only 14 of 369 samples had urea nitrogen values > 179 mmol/L (500 mg/L) (5).
of the earliest and most convenient laboratory indicators of acidosis is an increased anion gap (7), and these falsely increased chloride values will clearly disguise an abnormal anion gap in some renal failure patients. Thus, we have stopped reporting chloride values from the i-STAT analyzer in our outpatient surgery centers on the basis that no value is better than an erroneous value.

References