Do Serum Creatinine Levels Show Clinically Significant Fluctuations on Serial Determinations on the Siemens Advia 1800 Analyzer?

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Background: The goal of this work was to determine whether there are clinically significant fluctuations in the level of serum creatinine on serial determinations, especially in the borderline range (1.1–1.3 mg/dl), after specimen storage. **Methods:** Sixty-one serum samples were analyzed. They were divided into three categories based on the initial serum creatinine measurement: low (≤ 1.0 mg/dl), borderline (1.1–1.3 mg/dl), and high (≥ 1.4 mg/dl). The specimens were stored at 4°C and run on the Siemens Advia 1800 chemistry analyzer on days 1, 3, and 11. **Results:**

Statistical comparisons of the three groups were made using the unpaired *t*-test, yielding a two-tailed *P*-value for each group comparison. The *P*-values ranged from 0.0829 to 0.3892, indicating no statistically significant difference between the standard deviations of each group. **Conclusions:** Mild-to-moderate fluctuations in precision occur in successive serum creatinine determinations. The overwhelming majority of these fluctuations should not affect clinical decision making. *J. Clin. Lab. Anal.* 31:e22012, 2017. © 2016 Wiley Periodicals, Inc.

Key words: creatinine; reproducibility; serum; Siemens Advia 1800 analyzer; storage

INTRODUCTION

Over the past several years, we set out to evaluate the reproducibility of analyte determinations (measurements) on the Siemens Advia 1800 chemistry analyzer for quality assurance purposes. These experiments were a natural next step in determining the precision of said instrument after it supplanted the Advia 1650 analyzer, which was previously owned by the Bayer Corporation. In 2012, we proved that the Advia 1800 yields reliable and reproducible measurements of serum levels of the electrolytes sodium, potassium, chloride, and calcium (1). One year later, we performed the same analysis for serum glucose determinations, simultaneously elucidating which blood collection tubes give long-term stable measurements (2). When we extended the aforementioned studies to that of blood urea nitrogen (BUN) and creatinine measurements, we came up with mixed results (3). BUN determinations proved to be stable over a time

period of 15 days and a wide range of principal BUN values (6.0–83.0 mg/dl). However, although low and high creatinine values appeared to be reproducible over time, borderline primary values (1.1–1.3 mg/dl) were not as reproducible. In particular, half of the borderline principal values showed significant fluctuations and the greatest deviation from the mean among all initial creatinine values. One patient in particular had measurements which ranged from 1.1 to 1.5 mg/dl (reference range: 0.4–1.2 mg/dl) within the first 11 days of the experiment. Ostensibly, such values could lead to a diagnostic quandary, as the lower values represent normal kidney function, whereas the

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higher values point to renal insufficiency. Still, we were able to exploit BUN as an internal control for the patient's true renal status. Indeed, the patient's BUN determinations ranged from 10 to 11 mg/dl (reference range: 6–22 mg/dl) over the same time period used for creatinine measurements, supporting normal kidney function in this patient.

To investigate whether borderline serum creatinine values may be subject to larger fluctuations than for values that are normal or elevated, we compared, using larger sample sizes, the standard deviations for creatinine values in three different groups of patients: those with normal values, those with borderline values and those with well-defined elevated values. We present these results in this study.

METHODS

Sixty-one serum samples from patients at the New York Harbor VA Medical Center, Brooklyn Campus, were selected from patients who were collectively shown to have serum creatinine concentrations ranging from 0.4 to 8.4 mg/dl (reference range: 0.4–1.2 mg/dl). The serum samples were split into three groups—group 1: low (≤ 1.0 mg/dl), group 2: borderline (1.1–1.3 mg/dl), and group 3: high (≥ 1.4 mg/dl)—based on the value of the initial assay result of creatinine concentration for each sample. The breakdown of the 61 samples was as follows: 15, 31, and 15 specimens in each respective group. The specimens were stored at 4°C and run on the Siemens Advia 1800 chemistry analyzer on day 1, day 3, and day 11. As in the previous study, the creatinine determinations were made using the Jaffe method (based on the interaction between creatinine and picric acid). The means, standard deviations (SD), and percent coefficients of variation (%CV) were calculated for each of the sixty-one serum samples. At first, we looked for deviations from the mean of a magnitude comparable to that of the above example from the previous study in which a serum sample with a day 1 borderline creatinine value of 1.3 mg/dl dropped down to as low as 1.1 mg/dl, subsequently rising to as high as 1.5 mg/dl (SD of 0.14 mg/dl). Secondly, we separately compared the standard deviations of the three groups using the unpaired *t*-test in an effort to spot any statistically significant difference in deviation from the mean between the three groups. Statistical significance was inferred from a two-tailed *P*-value.

RESULTS

As can be seen in Tables 1–3, the serum creatinine level determinations for the three groups (i.e., low,

borderline, and high, respectively) on three select days (i.e., days 1, 3, and 11) fluctuated in all three patient groups. Included in each table are the mean, standard deviation, and percent coefficient of variation for each sample. During the period of study (July–August, 2015), the coefficient of variation for between-run results for the low control (mean, 0.6 mg/dl) was 5.3% and 3.0% for the high control (mean, 7.8 mg/dl). Only 2/61 samples showed 100% reproducibility, samples 14 and 24 in Table 2; both specimens were in the borderline group.

Most of the other serum creatinine values either increased or decreased from the original measurement by 0.1 mg/dl (10/15 samples in Table 1; 21/31 samples in Table 2; 9/15 samples in Table 3). Sometimes, the serum creatinine values both increased and decreased from the original measurement by 0.1 mg/dl over the three measurements taken for each sample (3/15 samples in Table 1; 6/31 samples in Table 2; 2/15 samples in Table 3). Rarely, the serum creatinine values deviated from the original measurement by 0.2 mg/dl (1/15 samples in Table 1; 1/31 samples in Table 2; 3/15 samples in Table 3). Finally, some samples showed serum creatinine value changes of greater than 0.2 mg/dl from the original measurement. One sample in Table 1 showed an increase in serum creatinine of 0.3 mg/dl from the original measurement (1/15 samples in Table 1). One sample in Table 2 also showed a serum creatinine increase of 0.3 mg/dl (1/15 samples in Table 2). One sample in Table 3 showed a serum creatinine decrease of 0.5 mg/dl (1/15 samples in Table 3), the greatest deviation of all three groups.

The mean serum creatinine level determinations for the 15 samples from group 1 (Table 1) ranged from

TABLE 1. Group 1: Low primary creatinine values (≤ 1.0 mg/dl)

Sample	Day 1	Day 3	Day 11	Mean	SD	%CV
1	0.9	1	1.2	1.0333	0.1528	14.883
2	0.9	0.8	0.8	0.8333	0.0577	6.928
3	1	0.9	1.1	1	0.1	10
4	0.6	0.6	0.7	0.6333	0.0577	9.117
5	0.9	0.9	1	0.9333	0.0577	6.186
6	0.8	0.8	0.9	0.8333	0.0577	6.298
7	0.6	0.6	0.7	0.6333	0.0577	9.117
8	0.7	0.8	0.9	0.8	0.1	12.5
9	0.4	0.4	0.5	0.4333	0.0577	13.324
10	0.9	0.8	1	0.9	0.1	11.111
11	0.7	0.7	0.8	0.7333	0.0577	7.873
12	0.9	0.9	1.1	0.9667	0.1155	11.945
13	0.7	0.7	0.8	0.7333	0.0577	7.873
14	0.9	0.9	1	0.9333	0.0577	6.186
15	0.9	0.9	1	0.9333	0.0577	6.186

SD, standard deviation; %CV, percent coefficient of variation.

TABLE 2. Group 2: Borderline primary creatinine values (1.1–1.3 mg/dl)

Sample	Day 1	Day 3	Day 11	Mean	SD	%CV
1	1.1	1.4	1.4	1.3	0.1732	13.323
2	1.3	1.4	1.4	1.3667	0.0577	4.224
3	1.3	1.4	1.5	1.4	0.1	7.142
4	1.1	1.2	1.2	1.1667	0.0577	4.948
5	1.1	1.2	1.3	1.2	0.1	8.333
6	1.2	1.3	1.2	1.2333	0.0577	4.681
7	1.2	1.3	1.3	1.2667	0.0577	4.558
8	1.1	1.2	1.2	1.1667	0.0577	4.948
9	1.1	1.2	1.2	1.1667	0.0577	4.948
10	1.2	1.2	1.3	1.2333	0.0577	4.681
11	1.2	1.3	1.3	1.2667	0.0577	4.558
12	1.1	1.2	1.2	1.1667	0.0577	4.948
13	1.2	1.3	1.4	1.3	0.1	7.692
14	1.2	1.2	1.2	1.2	0	0
15	1.1	1.1	1.2	1.1333	0.0577	5.094
16	1.2	1.2	1.3	1.2333	0.0577	4.681
17	1.3	1.3	1.4	1.3333	0.0577	4.33
18	1.3	1.4	1.5	1.4	0.1	7.142
19	1.3	1.4	1.3	1.3333	0.0577	4.33
20	1.2	1.3	1.3	1.2667	0.0577	4.558
21	1.2	1.3	1.3	1.2667	0.0577	4.558
22	1.2	1.3	1.4	1.3	0.1	7.692
23	1.1	1.2	1.2	1.1667	0.0577	4.948
24	1.1	1.1	1.1	1.1	0	0
25	1.3	1.4	1.3	1.3333	0.0577	4.33
26	1.3	1.5	1.5	1.4333	0.1155	8.056
27	1.1	1.2	1.2	1.1667	0.0577	4.948
28	1.2	1.3	1.4	1.3	0.1	7.692
29	1.1	1.2	1.2	1.1667	0.0577	4.948
30	1.3	1.4	1.3	1.3333	0.0577	4.33
31	1.3	1.3	1.4	1.3333	0.0577	4.33

SD, standard deviation; %CV, percent coefficient of variation.

0.4333 to 1.0333 mg/dl. The standard deviations ranged from 0.0577 to 0.1528 mg/dl with a mean value of 0.07635 mg/dl. The percent coefficients of variation ranged from 6.186 to 14.883% with a mean percent coefficient of variation of 9.3018.

The mean serum creatinine level determinations for the 31 samples from group 2 ranged from 1.1 to 1.4 mg/dl. The standard deviations ranged from 0.0 to 0.1732 mg/dl. The mean standard deviation was 0.06775 mg/dl. The percent coefficients of variation ranged from 0.0 to 13.323%. The mean percent coefficient of variation was 5.321%.

The mean serum creatinine level determinations for the 15 samples from group 3 ranged from 1.3667 to 8.1667 mg/dl. The standard deviations ranged from 0.0577 to 0.2517 mg/dl. The mean standard deviation was 0.09032 mg/dl. The percent coefficients of variation ranged from 2.05 to 4.224%. The mean percent coefficient of variation was 3.425%.

We compared the standard deviations found for the creatinine values in each group with one another using

TABLE 3. Group 3: High primary creatinine values (≥ 1.4 mg/dl)

Sample	Day 1	Day 3	Day 11	Mean	SD	%CV
1	8.4	7.9	8.2	8.1667	0.2517	3.082
2	3	2.8	3	2.9333	0.1155	3.936
3	5.7	5.5	5.7	5.6333	0.1155	2.05
4	4.2	4.1	4.3	4.2	0.1	2.381
5	1.8	1.9	1.9	1.8667	0.0577	3.093
6	1.4	1.4	1.5	1.4333	0.0577	4.028
7	2.6	2.6	2.7	2.6333	0.0577	2.192
8	1.4	1.3	1.4	1.3667	0.0577	4.224
9	1.5	1.5	1.6	1.5333	0.0577	3.765
10	1.4	1.4	1.5	1.4333	0.0577	4.028
11	1.4	1.4	1.5	1.4333	0.0577	4.028
12	2	1.9	2.1	2	0.1	5
13	1.4	1.4	1.5	1.4333	0.0577	4.028
14	5.9	5.7	6	5.8667	0.1528	2.604
15	2	1.9	2	1.9667	0.0577	2.936

SD, standard deviation; %CV, percent coefficient of variation.

an unpaired *t*-test yielding a two-tailed *P*-value for each group comparison. *P*-values greater than 0.05 were considered to indicate no statistically significant difference between the standard deviations between two groups being compared. We found *P*-values of 0.39, 0.39, and 0.08 when comparing the normal group with the borderline group, the normal group with the high group, and the borderline group with the high group, respectively. These results indicate that there were no statistically significant differences between the standard deviations among the three different groups.

DISCUSSION AND CONCLUSION

The goal of this quality assurance study was to determine if there are significant fluctuations in borderline values for serum creatinine, i.e., values that occur near the upper limit of the reference range (1.2 mg/dl) that are larger than those encountered for values that are normal or elevated. Large fluctuations on the borderline can lead to the inability to determine whether a patient has evidence of renal failure.

In a prior study (3), in contrast to fluctuation results that we observed on other critical analytes (1–3), we found instances where borderline creatinine values changed from normal to elevated and vice versa. We therefore designed this study to determine if this finding was unique to borderline values of creatinine. To this end, we directly compared the fluctuations of the creatinine values and their standard deviations for patients with normal, borderline, and elevated values of creatinine with one another. We find that most of the deviations are relatively small (0.1 mg/dl), that occasional larger fluctuations (e.g., 0.3 mg/dl) occur within all three groups, and that there is no statistical

difference between the standard deviations of the three groups. When these fluctuations occur for borderline values, they may result in oscillations between normal and abnormal values, preventing definitive diagnosis of renal disease.

It was not the purpose of this study to determine the cause of the observed fluctuations in creatinine, but rather to investigate whether they were unique to borderline values. The causes of the fluctuations could be attributed to sample stability, analyzer performance, or both. From Tables 1–3, it may be observed that creatinine values almost always increased slightly over the 11-day period, making it unlikely that sample degradation occurred as this occurrence would be expected to cause a decrease in concentration. The between-run CVs for creatinine varied from 3% to over 5% for high and low controls, respectively. The within-run CV for creatinine is approximately 1% according to the published values for the Advia 1800 analyzer. As our study is based on a between-run approach (determinations performed on successive days), the between-run CV of 5.3% for the low, normal values for creatinine is compatible with

fluctuations based on analyzer performance. Because, however, this changes to 3% for the high control, no definitive conclusion can be drawn regarding the origin of the observed fluctuations.

Based on our findings that there is no statistically significant difference in the standard deviations for the three groups, we conclude that there are no statistically significant differences in the reproducibility of serum creatinine levels among the three groups and that serum creatinine values determined on the Advia 1800 chemistry analyzer are reproducible and hence reliable.

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