

Short Communication

An investigation of enzymatic creatinine interference in a patient receiving dopamine and dobutamine

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ABSTRACT

Background: A laboratory investigation was initiated after a renal failure patient had a 2.18 mg/dL decrease in serum creatinine, which was not explained through medical intervention. The investigation revealed specimens providing questionably low results had been collected from a peripherally inserted central catheter (PICC) line. **Methods:** Patient specimens and serum pools were analyzed by the Siemens Vista enzymatic creatinine measurement procedure. A simulation of the patient's infusion protocol examined potential PICC line carryover and specimen collection technique.

Results: A simultaneously collected specimen set, arterial line and PICC line, yielded a difference of 1.86 mg/dL. Infusion and collection simulation studies suggested the most likely scenario was the infusion pump was not shut off while the specimen collection occurred and contaminated the specimen.

Conclusion: Providers should be aware of erroneously low creatinine results when administering catecholamine drugs and collecting specimens through the same catheter. The mechanism of specimen contamination is consistent with a siphoning effect from one lumen to the other during collection with the infusion pumps still running.

1. Introduction

Serum creatinine is a biomarker for estimating glomerular filtration rate (eGFR) in patients [1]. Serum creatinine results are input into estimating equations and provide clinicians with an assessment of renal function. Two laboratory creatinine measurement procedures are the Jaffe and the enzymatic reagent systems. The Jaffe reagents utilize picric acid to produce a colorimetric response and enzymatic reagents employ enzymes throughout the reaction. The Jaffe reaction's non-specificity is well documented [2–5]. Given these analytical specificity issues, laboratories are moving to enzymatic creatinine measurement procedures, which are viewed as more creatinine specific.

Reports of enzymatic creatinine reagents providing falsely low results when patients are receiving dopamine and or dobutamine have been published [6–12]. Karon et al. proposed two separate chemical mechanisms for this interference, both producing negative interference [9]. One was dopamine in the presence of peroxide reacts with assay reagents to produce a chromophore with a smaller absorptivity and falsely lowers signal. The other is in the presence of peroxidase,

dobutamine reacts with and depletes peroxide to levels inhibiting chromophore generation.

This study was pursued after an inpatient with renal failure had a 2.18 mg/dL decrease in serum creatinine with no medical intervention. The initial result was 4.25 mg/dL and 6 h later was 2.07 mg/dL. All creatinine measurements were obtained using the Siemens Dimension® Vista 1500 employing enzymatic creatininase reagents. Repeat specimen analysis on the laboratory's 2nd Vista instrument provided the same result. Further investigation revealed the specimens providing questionable results were collected from a peripherally inserted central catheter (PICC) line. During the third PICC line collection, a simultaneous arterial line specimen collection was analyzed by the Vista and provided values consistent with previous.

Specimen collection protocol, drug carryover studies and *in vitro* drug delivery simulations using the patient's same PICC line model and infusion rate were investigated.

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2. Materials and methods

2.1. Chemicals and reagents

Creatinine results were acquired on the Siemens Dimension® Vista 1500 (Siemens Healthcare Diagnostics Inc. Tarrytown, NY USA) and Abbott i-STAT® (Abbott Point of Care Inc. Princeton, NJ USA) systems and testing was performed per manufacturer's instructions.

2.2. Infusion simulation studies

A 60 cm 4 French Dual-Lumen Polyurethane Catheter reorder number 3264155 (Bard Access Systems, Inc., Salt Lake City, Utah USA) PICC line was used. Dopamine HCL 400 mg/250 mL (Baxter Deerfield, Illinois, USA) and Dobutamine 500 mg/250 mL (Baxter) were infused at 430 µg/min through the PICC line using a Sigma Spectrum Infusion Pump (Baxter) into a waste beaker for 2 h. The infusion rate matched the patient's. Fresh frozen plasma (FFP) was acquired from the University of Minnesota Medical Center (UMMC) Fairview Blood Bank and was used for draw simulations. Collections were obtained by stopping the infusion, clamping the infusion port, wiping the infusion line with an isopropanol pad Alcohol Prep Webcol (Covidien USA), and placing into the plasma bag. *In vitro* simulated draws and infusions were performed in the red collection port and gray infusion port, respectively. Simulated collections were taken out of the infusion port in noted instances. The UMMC specimen collection for a PICC line draw protocol was followed: pull and discard 5 mL of blood (waste) using a 10 mL syringe (Luer-Lok Tip NJ, USA) followed by pulling 3–5 mL of blood (draw) with a 10 mL syringe and transfer to a 12 × 75 SP™ Brand AccuTube™ polypropylene collection tube (Cardinal Health McGaw Park, IL USA). The line was flushed with 0.9% Sodium Chloride Injection USP (BD PosiFlush NJ, USA) after collections. Line ports were wiped with isopropanol pads before and after collections. Infusion simulation specimens were analyzed within 10 min of collection on the Vista and i-STAT. The simultaneous infusion/collection study consisted of infusing 430 µg/min of dopamine and dobutamine directly into the plasma bag for 1 min. At one minute, the above collection protocol was followed.

2.3. Data analysis

Data were analyzed and graphed using Microsoft Excel software (Redmond, WA).

3. Results

The patient's creatinine results are plotted in Fig. 1 for both platforms. The i-STAT results were acquired 24–48 h after the initial Vista analysis.

Dopamine and dobutamine interference was examined in spiking experiments and details are given in the supplemental section.

The *in vitro* infusion simulation results are given in Table 1. Control specimens prior to infusions verified the transit through the catheter's lumen did not impact the creatinine results. The “waste” and “draw” specimens were analyzed on both the Vista and i-STAT platforms. Specimens were analyzed from the collection and infusion ports in an attempt to discern from which port specimens could have been collected. Table 1 shows a Vista result observed to decrease as the infusion port waste collection specimen (0.7 to 0.2 mg/dL). This specimen when analyzed by the i-STAT was found to increase slightly from 0.7 to 0.9 mg/dL. Using the line collection protocol, the draw specimen returns to ~0.7 mg/dL for the Vista and i-STAT. Infusion of dopamine and dobutamine at 430 µg/min directly into the plasma bag for 1 min was the final experiment. Waste and draw specimens were taken from the collection port during this infusion. The creatinine levels decreased for both waste and draw collections on the Vista platform from 0.69 to

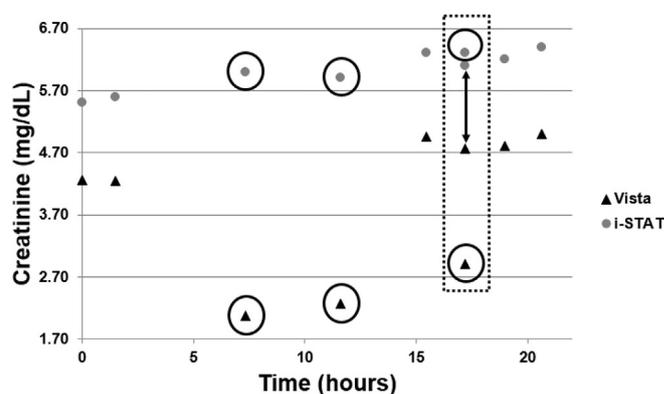


Fig. 1. Sample comparison of creatinine results over time using the Siemens Vista (triangles) and Abbott i-STAT (solid circles). Circled data points indicate PICC line draw specimen results. Dashed box indicates results from simultaneous PICC line and arterial line specimen collection. The arrow points to the arterial line collection specimen results.

0.27 mg/dL. The i-STAT values for the same specimens remained at 0.7 mg/dL.

4. Discussion

The patient's creatinine results suggest low Vista results occur from PICC line collections. When examined by the i-STAT, no decrease was observed, rather an increasing creatinine trend was seen fitting the clinical situation. Paired arterial line (4.7 mg/dL) and PICC line (2.9 mg/dL) draws at 17.2 h showed a 1.8 mg/dL difference suggesting an analytical interference with the specimens collected from the PICC line. Upon medical record examination, the patient was receiving a dopamine and dobutamine infusion through the PICC line during the collections. Dopamine and dobutamine have been shown to cause falsely low results for enzymatic creatinine measurement procedures [6–12]. Reviewing Vista and i-STAT package inserts reveals the general assay mechanism is identical throughout the first three steps [13,14]. The i-STAT performs electrochemical oxidation of H₂O₂ at the end of the third step and the Vista performs an additional step using peroxidase to produce a chromogen. Thus, the Vista's much lower measured creatinine concentrations in the presence of dobutamine or dopamine appears consistent with interference in final chromophore production as suggested by Karon et al. [9]. Also, negative creatinine interference with dopamine on the Vista has been documented [12]. Discrepancy between the Vista and i-STAT values in non-contaminated specimens are likely due to calibration differences between the measurement procedures as has been previously reported [15,16].

Two things investigated were: lack of following the standard PICC line blood collection protocol and/or PICC line carryover. Either seemed plausible; however discussion with the nursing staff suggested they followed the protocol as written. Sample analysis problems have been reported for other compounds when acquiring blood specimens from catheters [17,18]. The PICC line configuration was the 2 lumens were separated ran the entire catheter length. *In vitro* infusion experiments examined the collection protocol vs. drug line carryover. Control experiments suggest no inhibitory effect from the PICC line itself, and results were similar between both the Vista and i-STAT systems. After a 2 h infusion with the pumps stopped, *in vitro* waste and draw specimens from the collection port gave similar results on both measurement procedures with no decrease in creatinine values as expected given the separate lumens. Drugs would need to diffuse through the plastic to contaminate specimens. Infusion port specimen collection shows the waste collection had a negative interference with the Vista going from 0.7 to 0.2 mg/dL, and an increased value by the i-STAT from 0.7 to 0.9 mg/dL. In this instance, both measurement procedures could produce

Table 1
In vitro infusion studies.

<i>In vitro</i> testing	Type and site of collection	Creatinine concentration	
		iSTAT (mg/dL)	Vista (mg/dL)
Infusion experiments	Red collection port - White infusion port		
Plasma only control - No infusion of dopamine or dobutamine	Waste collection - Red port	0.7	0.69
	Draw collection - Red port	0.6	0.68
2 h Dopamine dobutamine infusion into beaker through white infusion port	Waste collection - Red port (Pump stopped white port clamped)	0.7	0.66
	Draw collection - Red port (Pump stopped white port clamped)	0.7	0.70
2 h Dopamine dobutamine infusion into beaker through white infusion port	Waste collection - White port	0.9	0.22
	Draw collection - White port	0.7	0.68
1 min dopamine dobutamine infusion into FFP bag through white infusion port	Waste collection - Red port (infusion pump running)	0.7	0.27
	Draw collection - Red port (infusion pump running)	0.7	0.27

results which differ from the recommended creatinine error from interfering substances (0.1 mg/dL or > 10% difference) [19]. This suggests dopamine and dobutamine have potentially opposite effects between the measurement procedures. Dopamine is known to be subject to electrochemical oxidation [20] thus potentially elevating the i-STAT signal. However, in the draw collection from the infusion port, both measurement procedure results aligned with the original creatinine values. This suggests the negative response is not from collection protocol or drug line adsorption. Another mechanism of contamination is a siphoning effect from one lumen to the other with the infusion pump running during collection. This is quite possible since IV dopamine infusions are not stopped abruptly, as this could result in serious adverse effects even death [21]. Waste and draw specimens taken out of the collection port with the infusion pump still running were found to illustrate profound decrease in creatinine for the Vista, but the i-STAT results remained stable.

5. Conclusions

We conclude the potential mechanism for dopamine and dobutamine specimen contamination arises from specimen collection while the infusion pump is running, likely by a siphoning mechanism at the PICC line end. This fits nursing staff accounts and the context for dopamine infusions should not be abruptly stopped. Line contamination by carryover for either drug was not observed to suppress creatinine results. This information should be shared with phlebotomy and nursing staff, as collection during infusion could compromise a specimen for testing even using a dual lumen catheter.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinbiochem.2019.08.001>.

References

- [1] National Kidney Foundation, K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification, *Am. J. Kidney Dis.* 39 (2 Suppl 1) (2002) S1–266.
- [2] L.D. Bowers, E.T. Wong, Kinetic serum creatinine assays. II. A critical evaluation and review, *Clin. Chem.* 26 (5) (1980) 555–561.
- [3] K. Spencer, Analytical reviews in clinical biochemistry: the estimation of creatinine, *Ann. Clin. Biochem.* 23 (1986) 1–25 Pt 1.
- [4] H. Crocker, M.D. Shephard, G.H. White, Evaluation of an enzymatic method for determining creatinine in plasma, *J. Clin. Pathol.* 41 (5) (1988) 576–581.
- [5] C.M. Cobbaert, H. Baadenhuijsen, C.W. Weykamp, Prime time for enzymatic creatinine methods in pediatrics, *Clin. Chem.* 55 (3) (2009) 549–558.
- [6] J.A. Weber, A.P. van Zanten, Interferences in current methods for measurements of creatinine, *Clin. Chem.* 37 (5) (1991) 695–700.
- [7] T.M. Daly, K.C. Kempe, M.G. Scott, "Bouncing" creatinine levels, *N. Engl. J. Med.* 334 (26) (1996) 1749–1750.
- [8] K.T. Koprowicz, D.S. Ooi, J.G. Donnelly, Influence of dopamine on peroxidase-based assays, *Clin. Chem.* 42 (9) (1996) 1502.
- [9] B.S. Karon, T.M. Daly, M.G. Scott, Mechanisms of dopamine and dobutamine interference in biochemical tests that use peroxide and peroxidase to generate chromophore, *Clin. Chem.* 44 (1) (1998) 155–160.
- [10] M. Peake, M. Whiting, Measurement of serum creatinine—current status and future goals, *Clin. Biochem. Rev.* 27 (4) (2006) 173–184.
- [11] A.K. Saenger, C. Lockwood, C.L. Snozek, et al., Catecholamine interference in enzymatic creatinine assays, *Clin. Chem.* 55 (9) (2009) 1732–1736.
- [12] A.K. Petrides, M.A. Ness, D.P. Judge, L.J. Sokoll, M.A. Marzinke, Fluctuating creatinine in the cardiac unit, *Clin. Chim. Acta* 447 (2015) 52–54.
- [13] Inc. SHD, Siemens Dimension Vista Enzymatic Creatinine, (2015).
- [14] Inc. APoC (Ed.), Abbott i-STAT Creatinine, Inc. APoC, 2015.
- [15] C. Papadea, J. Foster, S. Grant, et al., Evaluation of the i-STAT portable clinical analyzer for point-of-care blood testing in the intensive care units of a university children's hospital, *Ann. Clin. Lab. Sci.* 32 (3) (2002) 231–243.
- [16] J.H. Nichols, C. Bartholomew, A. Bonzagi, J.L. Garb, L. Jin, Evaluation of the IRMA TRUpoint and i-STAT creatinine assays, *Clin. Chim. Acta* 377 (1–2) (2007) 201–205.
- [17] S. Boodhan, A.M. Maloney, L.L. Dupuis, Extent of agreement in gentamicin concentration between serum that is drawn peripherally and from central venous catheters, *Pediatrics* 118 (6) (2006) e1650–e1656.
- [18] D.F. Wright, H.S. Al-Sallami, P.M. Jackson, D.M. Reith, Falsely elevated vancomycin plasma concentrations sampled from central venous implantable catheters (portacaths), *Br. J. Clin. Pharmacol.* 70 (5) (2010) 769–772.
- [19] N. Greenberg, W.L. Roberts, L.M. Bachmann, et al., Specificity characteristics of 7 commercial creatinine measurement procedures by enzymatic and Jaffe method principles, *Clin. Chem.* 58 (2) (2012) 391–401.
- [20] M.D. Hawley, S.V. Tatawawadi, S. Piekarski, R.N. Adams, Electrochemical studies of the oxidation pathways of catecholamines, *J. Am. Chem. Soc.* 89 (2) (1967) 447–450.
- [21] Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: advanced cardiovascular life support: section 6: pharmacology II: agents to optimize cardiac output and blood pressure. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation, *Circulation* 102 (8 Suppl) (2000) I129–I135.