

ACID-BASE AND ELECTROLYTE TEACHING CASE

Spurious Hyperphosphatemia in Patients on Hemodialysis With Catheters

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INDEX WORDS: Hyperphosphatemia; spurious hyperphosphatemia; alteplase; catheter; hemodialysis.

Hyperphosphatemia is an important independent risk factor for both cardiovascular calcification and cardiovascular morbidity and mortality in dialysis patients.¹⁻³ Serum phosphate levels are monitored routinely in patients on maintenance dialysis therapy, with high levels usually ascribed to nonadherence to diet or oral phosphate binders.

We report a case of pseudohyperphosphatemia caused by a contaminated blood sample obtained from a hemodialysis (HD) catheter. An absurd value found in a routine sample led us to investigate the reason for this result. We found that even minor apparent increases in measured phosphate levels may be caused by contamination when obtaining preanalytical specimens from HD catheters.

CASE REPORT

Clinical History

An 83-year-old woman with end-stage renal disease caused by renal artery stenosis and atheroembolism after attempted renal angioplasty in April 2006 is on long-term HD therapy 3 times weekly through a tunneled central venous catheter. Her comorbid conditions include type 2 diabetes, hypertension, dyslipidemia, and hypothyroidism. Her medications include losartan, amlodipine, metoprolol, levothyroxine, pantoprazole, sertraline, clopidogrel, atorvastatin, allopurinol, and vitamins. She receives epoetin alfa, 3,300 units, with each HD treatment, but is currently not treated with vitamin D or cinacalcet. Her catheter is occasionally locked with alteplase, 1 mg/mL, after HD treatments to prevent clotting and thus ensure adequate blood flow for dialysis.

Routine monthly laboratory tests showed that phosphate levels had been very well controlled with calcium acetate, 667 mg, 2 tablets 3 times daily, with phosphate values in the range of 3.1 to 5.5 mg/dL (1 to 1.78 mmol/L) and parathyroid hormone values in the low-normal range of 40 to 120 pg/mL (ng/L) since starting renal replacement therapy. It was noted that the patient had a reported serum phosphate level of 10.1 mg/dL (3.26 mmol/L; Fig 1) without change in diet and while maintaining strict adherence to her phosphate-binder regimen. A repeated phosphate test 1 month later showed an absurd value of 35.7 mg/dL (11.53 mmol/L). At this time, her calcium level was 8.4 mg/dL (2.1 mmol/L), within the normal range. The patient's clinical status was

unchanged at the time, and she insisted there had been no change in diet or medication adherence.

The laboratory result was verified by quality control in the laboratory, and no precision/accuracy issues were found. The patient's dialysis unit stated that the blood samples had been drawn from the catheter according to the unit's protocol by discarding the first 5 mL of blood obtained from both the venous and arterial ports. We hypothesized that the high phosphate content of the alteplase solution in the catheter was contributing to the increased phosphate levels in these samples.

Additional Investigations

As a first experiment, small amounts of alteplase were added to a normal control plasma sample with a measured baseline phosphate value. Phosphate was measured using the Olympus AU5400 analyzer (Olympus America Inc, Center Valley, PA) with the phosphomolybdate complex method. Amounts of 35, 70, or 105 μ L of alteplase were added to 1 mL of whole blood from a healthy volunteer.

Results are shown in Fig 2. Increases in phosphate values occurred in a linear fashion and were dramatic given the small volume added. Such volumes, the equivalent of about 1 to 3 drops, could easily contaminate the blood sample without being noticed by the health care professional.

As a second experiment, 8 mL of blood was drawn in serial 2-mL aliquots from each port of a tunneled central venous catheter from a second HD patient, an 82-year-old woman, whose catheter had been locked with alteplase after the previous dialysis treatment. In each 2-mL sample, phosphate was measured to detect contamination of the samples with alteplase.

The results (Table 1) clearly show a very dilute first sample with excessively high phosphate levels and inappropriately low sodium levels. Phosphate levels were increased even after the fill volume of the catheter was removed, most

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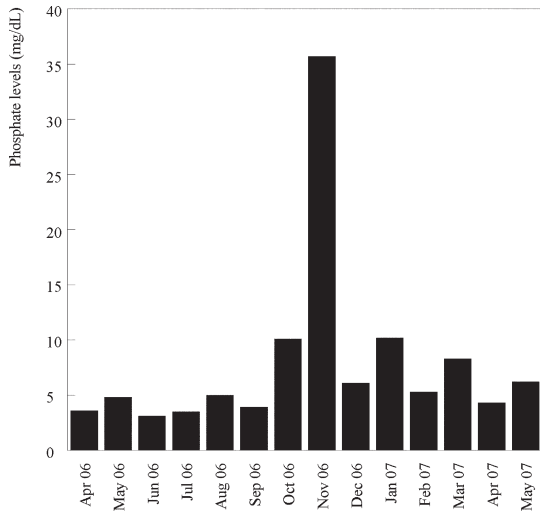


Figure 1. Routine phosphate results from patient 1 during 12 months. To convert plasma phosphate in mg/dL to mmol/L, divide by 0.3229.

likely because the blood obtained as the “fill volume” represents not only the blood contained in the catheter lumen, but also admixed blood drawn into the catheter through either the end hole or side holes during aspiration.

Therefore, to clear the catheter lock completely, a volume greater than the fill volume must be aspirated and discarded. To avoid unnecessary blood loss in patients with end-stage renal disease, we recommend the procedure described in the following section.

DISCUSSION

Unexplained hyperphosphatemia in patients on dialysis therapy most often is blamed on nonadherence to dietary restrictions or phosphate binders. In patients with a central catheter

Table 1. Sodium and Phosphate Content of Consecutive 2-mL Aliquots Drawn From Venous and Arterial Ports of the Tunneled Catheter in Patient 2, in Whom the Hemodialysis Catheter Had Been Locked With Alteplase

	Arterial		Venous	
	Sodium (mmol/L)	Phosphate (mg/dL)	Sodium (mmol/L)	Phosphate (mg/dL)
First 2 mL	68	161.5	63	177.3
Second 2 mL	135	9.56	136	9.69
Third 2 mL	136	6.47	136	5.95
Fourth 2 mL	137	5.68	137	5.58

Note: To convert phosphate in mg/dL to mmol/L, divide by 0.3229, sodium levels expressed in mmol/L and mEq/L are equivalent.

as HD access, the differential diagnosis of hyperphosphatemia must include the use of tissue plasminogen activator, which may erroneously increase blood phosphate levels because of an improper drawing technique. Tissue plasminogen activator commonly is administered as a catheter lock between dialysis treatments in patients with catheters that achieve only suboptimal blood flow rates because of clot formation in the catheter clogging the end or side ports. Because the longevity of catheters often can be prolonged with this approach, the technique is commonly used and considered safe, especially in patients in whom catheters are the last resort for access. A review of the literature showed 1 pediatric case report in which differences between peripheral and central blood samples led

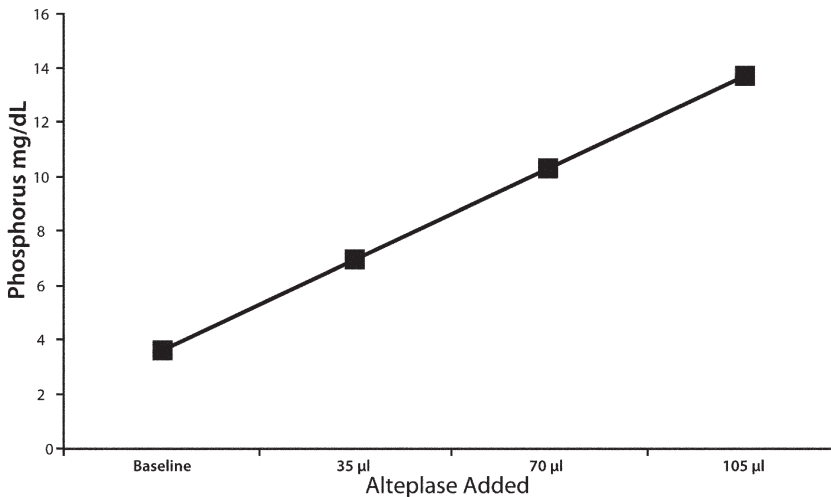


Figure 2. Phosphate levels in blood from a healthy volunteer measured in a 4.5-mL blood volume. Baseline plus the result after the addition of 35, 70, and 105 µL of alteplase show a linear increase in phosphate concentrations. To convert phosphate in mg/dL to mmol/L, divide by 0.3229.

to the detection of the same issue of unexplained increased phosphate levels.⁴

The label for the alteplase product administered does not give a specific phosphate content, but states that phosphoric acid is used for pH adjustment.

Our concern that contamination may occur more frequently than realized was confirmed by review of routine monthly phosphate levels during 12 months from patient 2. Phosphate levels in samples obtained after the catheter had been locked with alteplase resulted in greater mean phosphate levels, with a wider range (phosphate, 9.0 ± 2.5 mg/dL [2.91 ± 0.81 mmol/L]; range, 4.6 to 14.0 mg/dL [1.49 to 4.52 mmol/L]) compared with days when no alteplase was present (phosphate, 6.0 ± 1.4 mg/dL [1.94 ± 0.45 mmol/L]; range, 3.9 to 11.8 mg/dL [1.26 to 3.81 mmol/L]; Fig 3; the 1 single outlier value of 11.8 mg/dL [3.81 mmol/L] was obtained after the patient had skipped 2 consecutive HD treatments). During this time, calcium carbonate was used as phosphate binder,

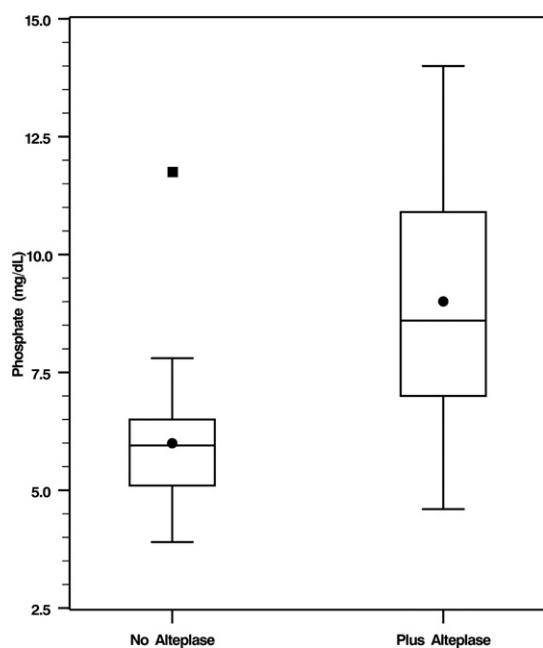


Figure 3. Whiskers plot of phosphate levels from patient 2 during 1 year on days that alteplase had been instilled into the catheter and on days without alteplase. The mean and range of the values are higher on days after alteplase compared with draws on days without alteplase. The single outlying value of 11.8 mg/dL (closed square) was obtained after the patient skipped 2 consecutive hemodialysis sessions during vacation. To convert phosphate in mg/dL to mmol/L, divide by 0.3229.

2 pills with each meal. A 4-week trial of lanthanum carbonate in response to phosphate levels of 10.7 to 12.5 mg/dL (3.46 to 4.04 mmol/L) during this period was stopped because of the “lack of effectiveness.” However, phosphate measurements during this time were obtained after use of alteplase. Therefore, increased phosphate levels secondary to alteplase contamination is likely.

Our results show that the practice of simply drawing and discarding a volume of blood equal to the volume of the catheter lumen before drawing the blood sample will lead to contaminated laboratory samples. Clearly, this concern arises with any catheter lock solution, not only alteplase. In the case of patient 1, it is clear from the extremely high phosphate level found that the unit protocol of discarding the first 5 mL of blood aspirated from the catheter before obtaining these samples was not followed.

The Clinical and Laboratory Standards Institute recommends that in drawing blood from an indwelling catheter or vascular access device (VAD), “the line should be flushed with 5 mL of saline, and the first 5 mL of blood or 6 dead-space volumes of the VAD discarded.”⁵ Adapting this recommendation to a patient with end-stage renal disease with a tunneled catheter, and with due regard to our results, we recommend drawing and discarding 5 to 6 mL of blood from each port as is routine practice, with strict reinforcement of this procedure among all care providers. It is possible that a catheter tip clot may make contamination more likely because drawing blood through the catheter side holes will facilitate contamination with alteplase. We therefore recommend “rinsing” the catheter immediately after the 5- to 6-mL of blood has been discarded by attaching a 10-mL syringe and withdrawing and reinfusing 10 mL of blood before drawing laboratory samples to eliminate any possibility of contamination.

Finally, it is important to note that spurious hyperphosphatemia also has been described in samples contaminated with heparin.⁶ Therefore, this issue may be even more common than recognized. Spurious hyperphosphatemia also has been reported with hyperbilirubinemia, hemolysis, paraproteinemia, and hyperlipidemia because in all these conditions, interference with the assay can occur.⁷⁻⁹ These possibilities were excluded in this patient.

We conclude that adherence to strict blood draw procedures from HD catheters is necessary to avoid contaminated samples resulting in misleading laboratory values.

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