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Heparin interference in whole blood sodium measurements in a pediatric setting

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Abstract

Objectives: In a pediatric setting, the incomplete filling of heparinized syringes is not an uncommon occurrence and has led to reports of falsely low hyponatremia in our institution. Little is known about heparin interference on sodium determination in whole blood, and our study aimed to investigate this interference due to excessive concentrations of heparin in pediatric specimens.

Design and methods: Three different types of syringes were filled with various amounts of blood to mimic greater than normal concentrations of heparin. Specimens were analyzed on an ABL 725 blood gas analyzer, and corresponding plasma fractions were analyzed on a VITROS 950 chemistry system. In a separate study, paired patient samples consisting of a capillary tube and microtainer clot were similarly analyzed.

Results: The presence of lithium heparin at 100 units/mL in blood caused a significant negative bias of 2–3 mmol/L in sodium concentration with the ABL 725, but no significant bias occurred when the corresponding plasma fraction was analyzed on the VITROS 950. For syringes containing electrolyte-balanced heparin, a similar negative bias was observed for blood but was not significant. Capillary tubes contained high concentrations of heparin (>100 units/mL) even when completely filled. Sodium results from capillary samples averaged 3.4 mmol/L lower than the corresponding serum values. These effects were independent of the sodium concentration across a wide range.

Conclusions: Small blood volumes collected with heparinized sampling devices in pediatric samples lead to excess heparin that may significantly affect sodium determinations and spur false reports of critical hyponatremia.

Keywords: Heparin; Sodium; Hyponatremia; Pediatrics; Syringes; Blood specimen collection; Blood gas analysis

Introduction

Heparin continues to be a highly reliable anticoagulant used for whole blood anticoagulation despite a long history of pre-analytical interferences due to dilution error, ion binding (notably calcium) and electrolyte distortion due to the release of bound ions [1–3]. While the current usage of dry heparin has virtually eliminated errors arising from sample dilution, the availability of various new preparations of heparin intended to overcome such problems has been met with mixed success [4]. Although its ability to interfere with ionized calcium measurements has been recognized, lithium heparin remains widely used as it is generally less expensive than electrolyte-balanced preparations of heparin.

Little attention has been given to interference by heparin on sodium determinations, particularly in whole blood. Previous reports have noted that, with concentrations of heparin at 100 U/mL, clinically significant negative biases are observed [5,6]. Concerns over the interference in ionized calcium determinations have greatly overshadowed apparent hyponatremia in cases of excessive heparin. Modest levels of heparin have been found to interfere with ionized calcium leading to proposals that final concentrations should not exceed 10–15 U/mL for lithium heparin [1,3,4], and several manufacturers now supply preparations which contain less heparin. In pediatric settings, however, the risk of sample clotting is much higher than the general population, and the use of collection devices with reduced heparin may not be practical.

Blood gas analysis plays an important role in the critical care setting where fast turnaround time is required. Since small sample

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volumes are sufficient for testing, clinical personnel tend to submit syringe samples that are incompletely filled. As a result, higher than normal concentrations of heparin are encountered which may interfere with certain assays. In this paper, we examine how the incomplete filling of syringes, not an uncommon occurrence among neonates in intensive care, and also how capillary samples may contain high concentrations of heparin that give rise to falsely lowered sodium determinations in whole blood.

Materials and methods

Syringes and capillary tubes

Three types of syringes with different heparin preparations were examined in the study. The Aspirator and Gaslyte syringes (Marquest Medical Products, Englewood, CO) hold 3 mL of sample and contain dry lithium heparin of 100 units and 7 units of heparin activity, respectively. The PICO50 syringes (Radiometer America, Westlake, OH) hold 2 mL of sample and contain dry electrolyte-balanced heparin (sodium/lithium heparin to which a specific concentration of calcium has been added) of 80 units of heparin activity. Capillary tubes (Bayer Diagnostics, Tarrytown, NY) hold 140 μL of sample and contain dry heparin with 18–28 units of heparin activity. Heparin activity was determined by filling containers with citrated plasma, and the contents were allowed to mix. The eluate was assayed by the anti-Xa chromogenic substrate methodology on the Behring Coagulation System (Dade Behring, Deerfield, IL).

Specimen collection and analysis

Initial studies were performed with venous blood from healthy adult volunteers after informed consent. To analyze the effect of incomplete filling of each type of syringe, ~14 mL of blood was drawn into plain red top tubes for each experiment. Immediately after collection, a portion was analyzed without any anticoagulant present. This served as the control specimen. The remaining blood was promptly transferred as follows: two syringes were filled to capacity, two were filled with 1 mL of blood, and four were filled with 0.5 mL of blood. Specimens were mixed thoroughly by hand, placed on ice and analyzed within 30 min. Specimens were analyzed on the ABL 725 blood gas analyzer (Radiometer A/S, Copenhagen, Denmark) according to manufacturer's instructions. Following whole blood analysis, the remaining sample in the syringe was collected individually, and the plasma fraction was obtained for sodium determination. In the case of the 0.5 mL filled syringes, it was necessary to pool the remaining blood in pairs. For the control sample, serum was collected from the clotted specimen. These samples were analyzed on the VITROS 950 chemistry system (Ortho-Clinical Diagnostics, Raridan, NJ).

To test the effect of lithium heparin on sodium measurements in patient samples, whole blood was obtained from leftover syringes containing >2.5 mL. The sodium concentration was reanalyzed prior to adding different amounts of heparin. From the remaining blood, 1 mL was transferred to a fresh syringe containing either 7 U or 100 U of heparin, mixed and the sodium concentration was remeasured on the ABL 725 blood gas analyzer.

For patient correlations, paired samples consisting of one capillary tube and one microtainer tube collected simultaneously from the neonatal intensive care unit were included in the study. The sodium result was recorded from routine analysis of blood gases, glucose and electrolytes from the capillary sample on the ABL 725. For the microtainer sample, serum sodium was appended to the requested analytes and measured on the VITROS 950 chemistry system.

Results

Our initial experiments sought to determine whether excess heparin, due to incomplete filling of syringes, interfered with sodium measurements in whole blood specimens. When the syringes were filled to the nominal capacity, only a slight decrease in the sodium result occurred for all types of syringes and was greatest for the sample in the Aspirator (standard heparin) syringe. However, these results were not statistically significant when compared to the uncoagulated whole blood control (Fig. 1). When the Aspirator syringe was filled to 1 mL (i.e. 1/3 full) at 100 U/mL of heparin, the measured sodium concentration decreased from 144.7 mmol/L to 141.2 mmol/L, which was statistically significant. A further decrease to 137.2 mmol/L occurred when filled to 0.5 mL with heparin at 200 U/mL. In contrast, the measured sodium concentrations were unaffected when incompletely filled Gaslyte (reduced heparin) syringes were tested in the same manner. The highest concentration of heparin was 14 U/mL, much lower than with the Aspirator syringe. Finally, the sodium measurement in the PICO50 (electrolyte-balanced heparin) syringe was not affected when filled to 1 mL (i.e. 1/2 full), but decreased to 142.6 mmol/L when the syringe was filled only to 0.5 mL at 100 U/mL of heparin. The amount of heparin in each preparation was confirmed by the Factor Xa assay, and only for the PICO50 did the amount differ from the manufacturer's stated value.

Several reports have demonstrated that high concentrations of lithium heparin cause a negative bias in the determination of

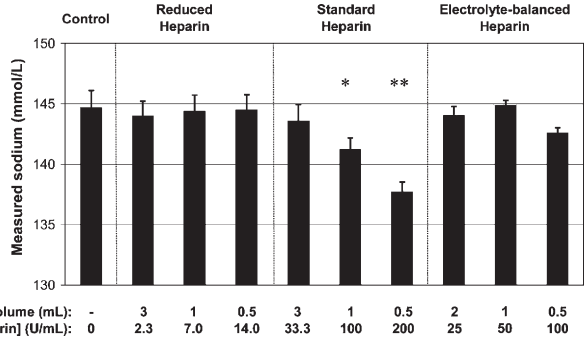

Fig. 1. Effect of heparin on whole blood sodium measurements in various heparinized syringes. Blood was drawn into each type of syringe with the stated volumes and the final concentration of heparin indicated. As a control, a fresh sample without any heparin was analyzed on the same instrument. Data are presented as mean ± 1 SD, $N = 6–10$ per group. Significant at $*P < 0.05$, $**P < 0.01$.