**Methodology**

**Vecuronium- and Esmolol-Induced Pseudohypernatremia Due to Drug Interference With Ion-Selective Electrodes**

Tracey G. Polsky, MD, PhD1,2; Eloise Salmon, MD3; Sarah S. Welsh, MD4,5; Derick Lim, MS, MLS(ASCP)1; Sheng Feng, PhD1,2; Lance Ballester, MS6; Abdulla M. Ehlayel, MD3; Jennifer L. Hewlett, PharmD7; Michelle R. Denburg, MD, MSCE2,3; Donald L. Boyer, MD, MSEd2,4; Ulf H. Beier, MD2,3

**Objectives:** We observed that patients treated with continuous vecuronium or esmolol infusions showed elevated plasma sodium measurements when measured by the routine chemistry analyzer as part of the basic metabolic panel (Vitros 5600; Ortho Clinical Diagnostics, Raritan, NJ), but not by blood gas analyzers (RAPIDLab 1265; Siemens, Tarrytown, NY). Both instruments use direct ion-selective electrode technology, albeit with different sodium ionophores (basic metabolic panel: methyl monensin, blood gas: glass). We questioned if the basic metabolic panel hypernatremia represents artefactual pseudohypernatremia.

**Design:** We added vecuronium bromide or esmolol hydrochloric acid to pooled plasma samples and compared sodium values measured by both methodologies. We queried sodium results from the electronic medical records of patients admitted at Children's Hospital of Philadelphia from 2016 to 2018 and received vecuronium and/or esmolol infusion treatment during their admissions.

**Setting:** PICU of a quaternary, free-standing children's hospital.

**Patients:** Children admitted to the hospital who received vecuronium and/or esmolol infusion.

**Measurements and Main Results:** Sodium was measured in pooled plasma samples by basic metabolic panel and blood gas methodologies after adding vecuronium bromide or esmolol hydrochloric acid, leading to a dose-response increase in basic metabolic panel sodium measurements. A repeated measures regression analysis of our electronic medical records showed that the vecuronium dose predicted the Δ sodium (basic metabolic panel–blood gas) sodium within 12 hours of the vecuronium administration (p < 0.0018). Esmolol showed a similar trend (p = 0.13). This occurred primarily in central line samples with continuous vecuronium or esmolol infusions.

**Conclusions:** Vecuronium and esmolol can falsely elevate direct ion-selective electrode sodium measurements on Vitros chemistry analyzers. Unexpectedly high sodium measurements in patients receiving vecuronium and/or esmolol infusions should be further investigated with an alternate sample type (i.e., peripheral blood) or measurement methodology (i.e., blood gas) to guide treatment decisions.

**Key Words:** hypernatremia; laboratory interference; methyl monensin; sodium measurement; Vitros

Sodium derangements occur relatively frequently in patients admitted to ICUs and can cause direct injury as cells are exposed to hypertonic or hypotonic stress, associated with an increased risk of morbidity or even death (1, 2). Accurate and rapid plasma sodium measurements are essential to guide therapeutic decisions. Under- or overestimating sodium can cause harm, especially since the treatment of either condition is often directly opposing (and if in error, exacerbating) the alternate condition. Consequentially, sodium measurements have long been a
central focus in clinical laboratory medicine throughout its history. These began with time-consuming zinc uranyl acetate precipitation in the 1920s (3). Sodium measurements were much accelerated with the introduction of flame photometers in the 1940s (4, 5). Flame photometry was eventually replaced by ion-selective electrode (ISE)-based measurements, which are more accurate and less interference-prone to blood lipids and proteins (6). Today, ISE measurements are widely used in clinical practice and are the standard of care. Clinicians have learned to rely on ISE measurements; however, even with modern ISE technology, there is still a potential for interference from biological components and drugs (7), which is important to recognize.

In this report, we show that vecuronium bromide and esmolol hydrochloric acid (HCl), two drugs commonly used in critical care for muscle relaxation and to lower blood pressure/reduce arrhythmia, respectively, were noted to be associated with pseudohypernatremia in ICU patients. Neither drug is known to be associated with ISE interference, but both caused pseudohypernatremia in plasma samples measured by the Vitros 5600 chemistry analyzer (Ortho Clinical Diagnostics, Raritan, NJ). We conducted laboratory experiments reproducing the pseudohypernatremia in vitro and performed an analysis from our electronic medical record to further define the scope of the problem. The possibility of drug-ISE interference may not be immediately obvious but it is important for clinicians to be aware of this possible finding as it has the potential to lead to inappropriate interventions in patients with falsely elevated sodium concentrations.

MATERIALS AND METHODS

Human Subjects
We retrieved the electronic medical records of patients admitted to Children’s Hospital of Philadelphia between 2016 and 2018 who received either esmolol HCl or vecuronium bromide during their hospitalization. Our electronic medical record review was approved by the Institutional Review Board (IRB) of the Children’s Hospital of Philadelphia, which waived the need for informed consent (IRB 18-015908).

Sodium Measurements
Basic metabolic panel (BMP) sodium measurements were performed on a Vitros 5600 or Vitros 4600 chemistry analyzer, as well as a Beckman Coulter AU 5822 (Beckman Coulter, Brea, CA). Blood gas (BG) sodium measurements were obtained on Siemens RAPIDLab 1265 BG analyzers (Siemens, Tarrytown, NY) in the central laboratory and by iSTAT (Abbott Point of Care, Abbott, Lake Bluff, IL) at the bedside, using the manufacturer’s reagents and parameters.

In Vitro Drug Spiking to Assess for Pseudohypernatremia
We pooled surplus deidentified plasma samples and obtained a baseline sodium measurement. We added esmolol HCl, vecuronium bromide, nicardipine HCl, labetalol HCl, or cisatracurium besilate to separate plasma pools and used different instruments to measure the sodium concentrations. We calculated expected sodium values using the known dilution factors and baseline sodium measurement of the pooled plasma samples. The Nicardipine HCl vial contained 75 mg sodium chloride in 10 mL (Na 128.3 mmol/L), and esmolol HCl was prepared in 0.9% normal saline (Na 154 mmol/L). These concentrations were factored into the expected sodium calculations.

Data Analysis
Data were analyzed using Microsoft Excel 16.24 (Microsoft, Redmond, WA), SAS 9.4 with SAS/STAT 15.1 (SAS Institute, Cary, NC), and GraphPad Prism 8.2 (GraphPad Software, San Diego, CA). Electronic medical record data included sodium measurements by BMP or BG, as well as vecuronium and esmolol infusions. We included only continuous infusions with weight-based dosing data into our analysis so that we could map infusion intervals with sodium measurements and adjust for patient size. For the multivariate analysis (Fig. 4), we used normally distributed generalized estimating equations (GEEs) with compound symmetry covariance that was estimated using the maximum likelihood estimator and empirical ses (8, 9) to predict the Δ sodium (BMP–BG) following within 12 hours of a vecuronium and/or esmolol dose. We determined Δ sodium by identifying BMP sodium measurements and ascertaining if BG sodium measurements occurred ± 12 hours before or after the BMP measurement. The closest BG measurement was taken to calculate the Δ sodium (BMP–BG). Next, we identified if the Δ sodium (BMP–BG) occurred within 12 hours after a vecuronium and/or esmolol dose. If multiple doses occurred, averages (means) were calculated. Sensitivity analyses were also conducted to confirm the results were maintained with adjustments for differences in time between drug and sodium measurements. For the analysis in Figure 5, we normalized data by calculating averages of sodium measurements by BMP, BG as well as average vecuronium bromide and/or esmolol infusion rates for each patient per day of admission. Data were tested for normal distribution using D’Agostino and Pearson testing. We used Spearman correlation to compare sodium measurements with vecuronium or esmolol doses. We determined dose-response curve associations through regression analysis. Data were displayed as mean ± sem or mean with 95% CI.

RESULTS

Initial Observations of Vecuronium- and Esmolol-Induced Pseudohypernatremia
An infant with autosomal recessive polycystic kidney disease received continuous renal replacement therapy (CRRT). Although on CRRT, laboratory studies became notable for rising sodium levels on routine BMP. Enteral feeding regimen had remained stable on fortified formula, the infant received no sodium chloride supplementation, and all CRRT bags had standard sodium concentration of 140 mmol/L. Medications included sildenafil, treprostinil, vecuronium, ketamine, and norepinephrine. Interestingly, there was significant discrepancy between the sodium levels on BGs (RAPIDLab 1265; Siemens, Tarrytown, NY) and BMP chemistry (Vitros 5600 Integrated Systems; Ortho Clinical Diagnostics, Raritan, NJ), with the BG results consistent with normonatremia. Of note, increasing vecuronium bromide infusion rate coincided with the patient’s rising BMP sodium measurements (Fig. 1A, 2020 • Volume 2 • e0073)
raising suspicions that the BMP sodium may be due to a drug interference with the sodium measurement. To further investigate if vecuronium caused BMP sodium measurement interference, we obtained blood samples from the sample patient pre- and post-dialysis filter. Vecuronium is water-soluble and small enough (without bromide: 557.84 g/mol) to be removed during CRRT. Post-filter sodium corrected back down to BG sodium measurements, below the dialysate sodium concentration, which could not be explained with genuine hypernatremia (Fig. 1B). We made similar observations in a second patient where the BMP sodium measurements returned to the BG baseline as soon as vecuronium therapy was discontinued (Fig. 1C). In a third patient on high-dose vecuronium bromide infusion (2.5 mg/kg/hr), we noticed a simultaneous BMP and BG sodium of 192 and 134 mmol/L from the central line, respectively, while a capillary BMP sodium was 135 mmol/L. In addition to vecuronium, we have also observed that esmolol HCl is capable of inducing a similar discrepancy between BMP and BG sodium measurements (10), with the esmolol infusion rate increasing measured BMP sodium (Fig. 1D). Together, these observations led to the hypothesis that vecuronium bromide and esmolol HCl may interfere with BMP measurements and cause pseudohypernatremia.

Pseudohypernatremia Can Be Replicated in Plasma Samples by Adding Vecuronium and Esmolol

To experimentally assess if vecuronium bromide and esmolol HCl can cause pseudohypernatremia, we added each medication separately to pooled plasma samples. We compared plasma BG (1265 RAPIDLab) and BMP measurements with the Vitros 5600, as well as a Beckman Coulter AU 5822 from the clinical laboratory at the Hospital.
We observed that both drugs affected BMP sodium measurements from the Vitros chemistry analyzer in a dose-dependent manner (Fig. 2A–C). We conducted additional drug-spiking experiments with other common ICU drugs: the calcium channel blocker nicardipine (Fig. 2D), as well as the vecuronium and esmolol drug class relatives, cisatracurium, and labetalol (Fig. 2, E and F). We did not observe such findings with nicardipine (Fig. 2D). Cisatracurium and labetalol did produce an increase in BMP sodium measurements, although only at higher doses (Fig. 2, E and F). Taken together, the drug-induced increase in sodium measurements suggested some form of drug interference with the ISE used in the Vitros chemistry instruments.

**Vecuronium and Esmolol Chemical Structures Do Not Reveal Overt Cause of ISE Interference**

Drugs can alter ISE-based measurements by forming complexes with the ionophore, binding electrolytes of interest, or by changing the behavior of the ion-selective membrane (7, 11). Benzalkonium is known to interfere with the Vitros sodium ISE (12). The structure of benzalkonium is notable for a quaternary ammonium group (Fig. 3A), a feature shared by vecuronium (Fig. 3B), but not esmolol (Fig. 3C). In fact, the molecules of esmolol and vecuronium are quite distinct in size and charge, and it is difficult to speculate how a similar effect can be reproducibly achieved by both drugs. One common feature shared by both drugs is the presence of “acetoxy” groups, CH$_3$-C(=O)-O-, with esmolol and vecuronium having one and two each, respectively, and vecuronium appearing to have stronger effects at equal doses (Fig. 2C). However, two of our three negative controls also have acetoxy-groups and one quaternary ammonium group (Fig. 3D–F). These inconsistent observations make it difficult to speculate on...
and vecuronium or esmolol administration, we generated dose-response curves (Fig. 5A) similar to our vecuronium/esmolol and plasma mixing studies (Fig. 2C). We consolidated our data by forming average sodium levels and drug doses per patient per day, which led to 3,469, 533, and 27 patient days with documented vecuronium, esmolol or both drugs with recorded weight-specific dosing rates, respectively. Although the curve fitting was far less optimal than in our equivalent in vitro studies (Fig. 2C), it is remarkable how closely both curves overlap, thus highlighting the relative difference between vecuronium and esmolol and their effect on BMP sodium measurements (Fig. 5B).

In conclusion, our clinical data show that vecuronium and esmolol dosing can affect BMP sodium measurements on Vitros instruments. Together with our in vitro studies and earlier clinical observations, these findings are consistent with vecuronium and esmolol causing drug-induced interference with BMP-sodium measurements on Vitros chemistry systems.

**DISCUSSION**

The electrochemical measurement of sodium by ISE is the most common method used in clinical laboratories today and is considered to be the gold standard. ISEs are used in automated chemistry analyzers as well as BG and point-of-care instruments. ISE has replaced older methods for sodium measurement, such as atomic absorption spectroscopy and flame emission spectroscopy, both of which are impractical today in the modern clinical laboratory due to increased safety and maintenance requirements. ISE-based methodologies have excellent accuracy and precision, rapid turnaround time and high sample throughput, operate at a reasonably low cost, and use small amounts of blood. The latter is especially important in pediatric hospitals (13, 14), but is useful everywhere (15).

The selectivity of an ISE for a particular electrolyte is determined by the composition of the ion-selective membrane. Ion-selective membranes can be composed of glass, crystalline, or polymeric materials. In particular, sodium electrodes may contain either sodium-specific glass or polyvinyl chloride membranes with sodium-specific ionophores, such as methyl monensin or other monensin derivatives (7). Although these materials are all selective for sodium, the particular ISE used varies by instrument manufacturer. The two primary methodologies used to measure sodium in this report, Vitros BMP and Siemens BG, use different sodium ISEs; the Vitros contains methyl monensin, while the Siemens BG ISE contains glass. Notably, the Beckman AU that we used as a third sampler, which did not show elevated sodium measurements

---

**Figure 5.** Dose-response curves of vecuronium and esmolol on basic metabolic panel (BMP) sodium. A. Vitros 5600 sodium measurements from patients in Figure 4 matched with esmolol or vecuronium treatment doses (normalized to mg/kg/hr). Solid lines indicate plotted regression curves. Dashed lines indicate 95% CIs of the best fit line. B. Overlay of fitted curves from Figure 5A and Figure 2C, showing a similar relationship between esmolol and vecuronium exposure and Vitros 5600 sodium measurements in vitro when drugs were added to plasma (right y-axis, lower x-axis) and in vivo, from patients treated with vecuronium or esmolol (left y-axis, upper x-axis).
We thank Diego A. Campos (Children’s Hospital of Philadelphia [CHOP]) for retrieving electronic medical record data. We thank David R. Vann (U Penn) and Michael J. Bennett (CHOP) for helpful suggestions and Reynaldo Caparros (CHOP) for laboratory support.

Supported, in part, by grant from the National Institute of Allergy and Infectious Diseases (AI095353), Lafey McHugh Foundation and American Society of Nephrology funding (to Dr. Beier). Portions of this work were supported by the Children’s Hospital of Philadelphia Pediatric Centers of Excellence in Nephrology funded by the National Institute of Diabetes and Digestive and Kidney Diseases (DK114786).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: beieru@email.chop.edu

ACKNOWLEDGMENTS

We thank Diego A. Campos (Children’s Hospital of Philadelphia [CHOP]) for retrieving electronic medical record data. We thank

REFERENCES

1. Overgaard-Steensen C, Ring T: Clinical review: Practical approach to hyponatraemia and hypernatraemia in critically ill patients. Crit Care 2013; 17:206
2. Sterns RH: Disorders of plasma sodium—causes, consequences, and correction. N Engl J Med 2015; 372:55–65
3. Barber HH, Klothoff IM: A specific reagent for the rapid gravimetric determination of sodium. J Am Chem Soc 1928; 50:1625–1631
4. Barnes RB, Richardson D, Berry JW, et al: Flame photometry a rapid analytical procedure. Ind Eng Chem, Anal Ed 1945; 17:605–611
5. Hald PM: The flame photometer for the measurement of sodium and potassium in biological materials. J Biol Chem 1947; 167:499–510
6. Worth HG: A comparison of the measurement of sodium and potassium by flame photometry and ion-selective electrode. Ann Clin Biochem 1985; 22(PT 4):343–350
7. Dimeski G, Badrick T, John AS: Ion selective electrodes (ises) and interferences—a review. Clin Chim Acta 2010; 411:309–317
8. Ware JH, Dockery DW, Spiro A 3rd, et al: Passive smoking, gas cooking, and respiratory health of children living in six cities. Am Rev Respir Dis 1984; 129:366–374
9. Terrell GR, Scott DW: Oversmoothed nonparametric density estimates. J Am Stat Assoc 1985; 80:209–214
10. Welsh S, Polsky T, Lim D, et al: 873: Pseudohyponatremia due to esmolol a novel case report of drug interference in laboratory testing. Crit Care Med 2018; 46:421
11. Bakker E, Pretsch E, Bühllmann P: Selectivity of potentiometric ion sensors. Anal Chem 2000; 72:1127–1133
12. Gaylord MS, Pittman PA, Bartness J, et al: Release of benzalkonium chloride from a heparin-bonded umbilical catheter with resultant factitious hypernatremia and hyperkalemia. Pediatrics 1991; 87:631–635
13. Widness JA, Madan A, Grindeanu LA, et al: Reduction in red blood cell transfusions among preterm infants: Results of a randomized trial with an in-line blood gas and chemistry monitor. Pediatrics 2005; 115:1299–1306
14. Jakacka N, Snarski E, Mekuria S: Prevention of iatrogenic anemia in critical and neonatal care. Adv Clin Exp Med 2016; 25:191–197
15. Myles N, von Wieligh J, Kyricou M, et al: A cohort study assessing the impact of small volume blood tubes on diagnostic test quality and iatrogenic blood loss in a cohort of adult haematology patients. Intern Med J 2018; 48:817–821
16. Koch TR, Cook JD: Benzalkonium interference with test methods for potassium and sodium. Clin Chem 1990; 36:807–808
17. Chow E, Fox N, Gama R: Effect of low serum total protein on sodium and potassium measurement by ion-selective electrodes in critically ill patients. Br J Biomed Sci 2008; 65:128–131
18. Blasutig IM, Jung B, Kulasingam V, et al: Analytical evaluation of the VITROS 5600 integrated system in a pediatric setting and determination of pediatric reference intervals. Clin Biochem 2010; 43:1039–1044