Case report

Case Report: LWMH use in elderly patient with normal kidney function affects serum sodium and potassium levels

Comment [R11]: Interesting articles by explaining the background of problems and cases that have existed from year to year. It will be interesting if the relationship between Na and K is explained in more detail.

Abstract

An 87-year-old female with a history of paraplegia/neurogenic bladder, chronic left leg wound infection, and recurrent UTI, was admitted with a primary problem of frequent falls and found to have COVID-19 infection. Upon admission, the patient was given enoxaparin for DVT prophylaxis for hypercoagulability due to COVID-19. After 3 days of initiation of enoxaparin, the patient experienced hyponatremia with trending upward levels of potassium. It was believed to be due to the furosemide and was discontinued. Despite furosemide discontinuation, the patient continued down trending of serum sodium and an uptrend of potassium occurred. After 24 hours of discontinued enoxaparin, the sodium and potassium levels plateaued. We believe this patient experienced LMWH-induced hypoaldosteronism.

Keywords: Enoxaparin, hyponatremia

Introduction

In hospitalized settings, LMWH or other heparin derived products are commonly used for a wide range of anticoagulant purposes such as: atrial fibrillation, deep vein thrombosis prophylaxis or treatment, pulmonary embolism, and more. Approximately 12 million patients per year in the United States alone have been administered with heparin or LMWH [1].

Some of the common side effects of enoxaparin include bleeding, bruising, and injection site reactions. However, rare immune response conditions can occur as well, such as heparin-induced thrombocytopenia (HIT). HIT occurs in approximately 0.5 to 1% of patients exposed to unfractionated heparin for medical and surgical indication, 0.1 to 0.5% in patients receiving low molecular weight heparin (LMWH). The frequent use of heparin puts a large number of patients at risk of HIT [2].

Rarer side effects such as hyponatremia and hyperkalemia have been reported to heparin and LMWH. The prevalence of this phenomenon reported is <1%. In 2011, a study evaluated patients receiving heparin and LMWH with cardiovascular disease and ischemic stroke, showing an increase in potassium levels and decrease in sodium levels compared to baseline. The study saw the change on the fifth day of therapy was increased with LMWH compared with heparin, but still not statistically significant. They concluded that hyperkalemia anticipated in renal impairment receiving heparin or LMWH. [3]

Severe COVID-19 infections may also cause hyponatremia. Recently, a few studies have reported an association with dyselectrolytemia such as hyponatremia, defined by serum sodium levels less than 135 mmol/L. Hyponatremia in settings with COVID 19 infection has been associated with increased risk of death. Moderate hyponatremia was identified in about 60% of patients with a severe COVID-19

infection associated with watery diarrhea. However, current studies are inconclusive about the role of COVID-19 in hyponatremia, though hyponatremia may show the severity of COVID-19 infection and indicate an unfavorable prognosis. [4]

The mechanism by which heparin or LMWH affects electrolytes is not well understood. However, it is believed that heparin induced hypoaldosteronism is the culprit. Heparin blocks an enzymatic step in the synthesis of aldosterone, and reduces aldosterone levels, which thereby reduces the resorption of sodium in the principal cells of optical collecting tubules and leads hyperkalemia with the reduced excretion of potassium [5, 6].

Case Report

An 87-year-old female, weighing 52.3 kg and height 170.8 cm with a history of paraplegia/neurogenic bladder, chronic left leg wound infection, and recurrent UTI, was found in her apartment on her bed. She was brought in by ambulance due to frequent falls. At the time of the emergency visit the patient tested positive for SARS-CoV-2. She was a nonsmoker and denied use of alcohol or any illicit drugs. Patient reported weakness as a contributing factor to her frequent falls. Allergies listed as trimethoprim in 2016 with unknown reaction. Her prior admission medications list was as follows: furosemide 20 mg tablets twice daily, amoxicillin-clavulanate 875 mg tablets every 12 hours for cellulitis, cholecalciferol 5000 IU oral capsules daily, ferrous sulfate 325 mg tablet daily, and gabapentin 300 mg capsule three times a day.

On initial presentation, her vitals were as follows: blood pressure of 188/80 mmHg, SpO2 88% on room air, was placed on 1 L of O2 nasal cannula, temperature of 98.1F, peripheral pulse rate 68, and respiratory rate 17. Not diagnosed with severe COVID-19. On physical examination, she was awake, alert, and oriented. No murmurs or any peripheral edema was noted. Cellulitis of the left lower extremity with bandage in place.

Pertinent studies from the time of admission included: sodium of 137 mmol/L (136 -145), potassium of 4.1 mmol/L (3.5 - 5.1), magnesium of 1.9 mg/dL (1.9-2.7), and calcium of 8.2 mg/dL (8.6 - 10.3), albumin of 3.0 gm/dL (3.5 - 5.7), ALP of 82 IntUnit/L (34-104), ALT of 87 Intunits/L (7 - 52), AST of 75 IntUnit/L (13- 39), CK of 1009 IntUnit/L (30 -223), CKMB of 14.3 ng/mL (0.6 - 6.3), TSH of 0.21 mIU/mL (0.45 - 5.33), T4 free of 1.70 ng/dL (0.6- 1.6), T3 free of 2.20 pg/mL (2.5- 3.9), serum creatinine of 0.8 mg/dL (0.6 - 1.2), blood urea nitrogen levels of 21 mg/dL (7-25), and eGFR of > 60 mL/min/1.73m^2.

Given the patient's presentation of possible underlying hypercoagulable state due to COVID-19 infection, per hospital protocol, enoxaparin was started with 40 mg daily subcutaneously on day 1. CT scan of cervical spine without contrast showed, no acute finding, large thyroid goiter, mild left pleural effusion. EKG showed sinus rhythm with possible intraventricular conduction delay, QTc of 473 ms. Home medications were started. Throughout her stay, the patient refused her scheduled home medication, gabapentin.

On day 3, sodium of 132 mmol/L, potassium of 3.9 mmol/L, serum creatinine of 0.7 mg/dL, magnesium of 1.5 mg/dL, calcium of 7.8 mg/dL, ALP of 105 IntUnit/L, ALT of 113 IntUnit/L, AST of 66 IntUnit/L. Electrolytes replacement therapy was started: one time dose of IV magnesium 2 grams and normal saline 1 L bolus infusion.

Patient oxygen demand was spontaneously required twice in her entire hospital stay for a short interval. On day 4, she was started on 2 L/min nasal cannula for a short period of time due to oxygen desaturation when experiencing coughing spells. However, after this event she did not require oxygen supplemental therapy onward. Her potassium of 4 mmol/L, sodium of 130 mmol/L, serum creatinine of 0.7 mg/dL, magnesium of 2.0 mg/dL, ALP of 105 IntUnit/L, ALT of 113 IntUnit/L, and AST of 66 IntUnit/L.

Day 5, sodium of 126 mmol/L , magnesium of 1.8 mg/dL, potassium of 4.2 mmol/L, ALP of 168 IntUnit/L, ALT of 206 IntUnit/L, AST of 162 IntUnit/L. Discontinued furosemide due to continued decline of serum sodium despite other electrolytes going up, received only a morning dose of furosemide 20 mg oral, started metoprolol 12.5 mg twice daily, due to blood pressure control and new onset of atrial fibrillation with RVR, heart rate of 122 b/min , troponin of 0.37 to 0.35 ng/mL (0- 0.05) trending down. Due to patient fall history, she is a poor candidate for anticoagulation.

Day 6, sodium of 127 mmol/L, potassium of 4.7 mmol/L, magnesium of 1.9 mg/dL, ALP of 151 IntUnit/L, ALT of 159 IntUnit/L, AST of 91 IntUnit/L. Atrial fibrillation with RVR resolved/controlled with metoprolol. Patient also reported feeling nausea, but no events of vomiting during her stay, treated with ondansetron 4 mg IV as needed.

Since hyponatremia continued, we suspected the electrolyte imbalance was enoxaparin induced. Day 7, sodium of 123 mmol/L, potassium of 4.9 mmol/L, serum creatinine of 0.6 mg/dL, magnesium of 1.6 mg/dL. Enoxaparin was discontinued and not given on this day. Patient received 500 ml normal saline bolus.

After 24 hours of discontinuation of enoxaparin, sodium went up. Day 8, sodium of 129 mmol/L, potassium 4.6 of mmol/L, serum creatinine of 0.6 mg/dL, magnesium 2.3 mg/dL, ALP of 126 IntUnit/L, AST of 96 IntUnit/L, AST of 46 IntUnit/L. 2 grams of sodium chloride tablets (1 gram BID) administered only for this day.

Day 9, sodium of 132 mmol/L, potassium of 4.8 mmol/L, magnesium of 2.0 mg/dL, serum creatinine of 0.7 mg/dL. Patient was discharged to a skilled nursing facility.

Discussion

LWMH-induced hyponatremia is a very rare occurrence. Heparin and LMWH, being a hormone that affects the enzymatic step in the synthesis of aldosterone, may cause hypoaldosteronism in some patients. The reduced reabsorption of sodium in the principal cells of optical collecting tubules can also lead to reduced excretion of potassium [5, 6]. Heparin induced hyperkalemia has been more common in the literature, with no reported effect on serum sodium levels. This can occur as early as 3-5 days of initiation of these medications [7]. A 1995 study concluded that aldosterone suppression results in natriuresis and decreases excretion of potassium in 7% of the patients [5]. However, this required additional factors related to renal dysfunction.

There are often possible alternative explanations in patients with hyponatremia. Our patient initially presented with electrolytes within normal limits. Her hyponatremia, which occurred on day 3, may have been attributed to her COVID-19 infection or the start of her home furosemide. LMWH-induced hypoaldosteronism was not considered in the differential diagnosis despite the abnormal electrolyte levels. Patient experienced both hyponatremia and trending up of serum potassium despite

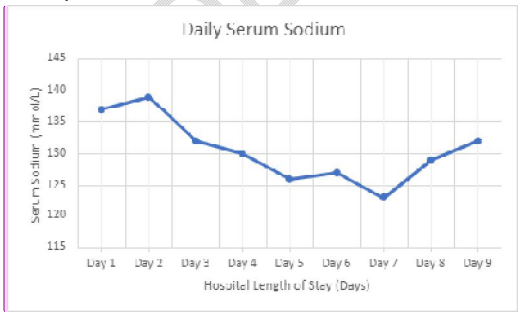
not having any potassium replacement or renal dysfunction. After enoxaparin had been discontinued for 24 hours, the serum sodium level increased with low intervention of sodium replacement of 500 mL of normal saline. The potassium level plateaued in the upper normal ranges(Shown on Figure 1). Patient's levels returned normal after 2-week follow-up from discharge date.

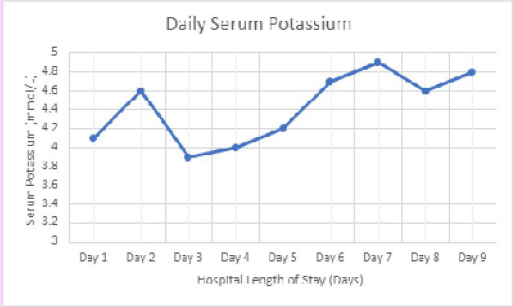
A 2020 study investigating use of salt tablets in treatment of euvolemic hyponatremia concluded that a small but significant improvement in serum sodium was observed compared to patients in the non-salt tablet group. After 48 hours the salt tablet group had an increase of 5.2 mEq/L than the non-salt tablet group of 3.1 mEq/L, p-value <0.001[8].

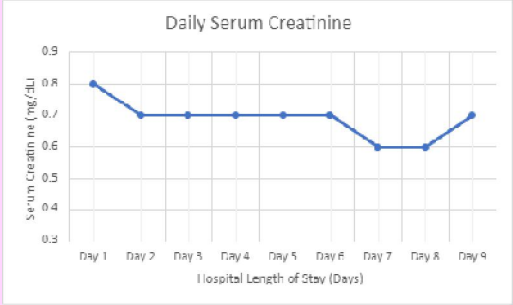
COVID-19 infection with severe acute respiratory syndrome has higher rates of interhuman transmission. COVID-19 infection has been associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH), reduced sodium ion intake or pharmaceutical induced [3]. Our patient had a COVID-19 infection; however, she experienced mild symptoms, which puts her at a lower risk of COVID-19 induced hyponatremia. This has been reported only in severe COVID patients, associated with having vomiting and/or diarrhea induced dyselectrolytemia. Our patient did not have any symptoms of vomiting or diarrhea. Another possible reason for SIADH in COVID-19 might be due to use of dexamethasone in supportive treatment. This was reported to have an effect of more than a week of hyponatremia [9].

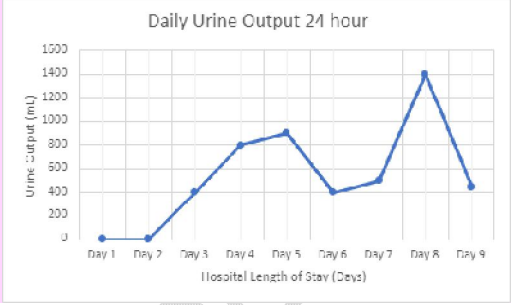
Determination of the etiology of hyponatremia and hyperkalemia is important in clinical outcomes. Depending on the patient with fluid restrictions, administering fluid sodium replacement might cause more morbidity and mortality.

Figure 1: Daily Serum Sodium - level of sodium was measured every morning since the time of admission. Daily Serum Creatinine - level of creatinine was measured since the time of admission. No major changes in renal function were noticed. Daily Serum Potassium - level of potassium was measured since time of admission, showing trending levels towards upper normal limit. No hemolysis occurred in samples.Daily Urine Output - measurements of urine were collected with "Purewick", external urine collection device. Day 1 and Day 2 collection was not reported.









Comment [R12]: It would be very good to convey data if the curve is presented in 1 figure, so that the causes and relationship between the decrease in Na levels and the increase in K levels can be compared.

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