Precipitation of hyponatremia and seizures by esmolol in sterile water formulation

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Purpose: Acute hyponatremia can lead to severe neurological symptoms such as confusion, obtundation, seizures, coma, and respiratory depression, contributing to increased morbidity and mortality. Patients with acute hyponatremia should be evaluated based on volume status and serum osmolality to determine potential causes and appropriate treatment. The aim of this case report is to illustrate the importance of using a multidisciplinary approach to evaluate medication formulation and the potential impact on a patient's clinical course.

Summary: A 34-year-old male was admitted for type A aortic dissection and was treated with an esmolol infusion and underwent operative repair. Two days after initiation of esmolol, the patient developed seizures and antiepileptics were initiated. The patient's serum sodium concentration was found to have decreased by a total of 14 mEq/L since admission. The patient had received more than 6 L of esmolol formulated in sterile water over the course of 2 days. The esmolol infusion was converted to another antihypertensive agent, and 0.9% sodium chloride injection was initiated, after which the serum sodium concentration began to recover. No further seizures were observed on continuous electroencephalography, and all antiepileptic drugs were discontinued with no seizure activity.

Conclusion: The esmolol product utilized in this case was formulated in 250 mL of sterile water, which is suspected to have contributed to the patient's hyponatremia. It is important to be aware of the formulation and excipients of medications and their potential for adverse effects.

Keywords: cardiology, education, hyponatremia, intensivist, neurology, seizure

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Acute hyponatremia can lead to severe neurological symptoms such as confusion, obtundation, seizures, coma, and respiratory depression, particularly with a rapid decline in serum sodium levels, contributing to increased morbidity and mortality. Patients with acute hyponatremia should be evaluated based on volume status and serum osmolality to determine potential causes and appropriate treatment. Hypovolemic hyponatremia may arise from diuretic use or gastrointestinal loss, euvolemic hyponatremia may be caused by excessive alcohol consumption or syndrome of inappropriate antidiuretic hormone (SIADH), and hypervolemic hyponatremia may result from heart failure or nephrotic syndrome. Treatment selection depends on both symptom severity and the class of hyponatremia, and therapy can involve fluid restriction, administration of isotonic or hypertonic saline, treatment with medications such as vaptans, or a combination of these.[1]

The aim of this case report is to illustrate the importance of using a multidisciplinary approach to evaluate medication formulation and the potential impact on a patient's clinical course.

Case report

We present the case of a 34-year-old Caucasian male who was admitted to

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our institution's emergency department for back pain and found to have type A aortic dissection. He had a medical history of hypertension, heart murmur, and attention deficit/hyperactivity disorder and was a current smoker. He was not taking any medications before admission. Nitroglycerin and esmolol infusions were initiated for blood pressure and heart rate control before the patient underwent operative repair. He was extubated on postoperative day 1 (POD1) and was started on oral metoprolol tartrate 25 mg by mouth twice daily but remained on nitroglycerin and esmolol. On the morning of POD2, the patient was noted to be somnolent. He was started on hydralazine 50 mg by mouth 3 times daily for additional blood pressure control. That evening, the patient had altered mental status, exhibited combative behavior, and was unable to follow commands or respond to questions. The neurology team was consulted and diagnosed the patient with seizures; levetiracetam and as-needed lorazepam were initiated. On POD3, seizure activity continued and the patient was subsequently reintubated. A midazolam infusion and fosphenytoin were initiated, and the levetiracetam dose was increased. On this day, the pharmacist noted a significant decrease in the patient's serum sodium level, with a total decrease of 14 mEq/L since admission, and evaluated the current medication list for contributing medications. The patient had required a significant amount of esmolol, and the hospital's esmolol formulation contained approximately 250 mL of sterile water for injection per bag (2,500 mg/250 mL). After reviewing that over 6 L of esmolol in sterile water for injection had been administered over the course of 2 days, the pharmacist recommended to the cardiovascular surgery team that they discontinue the esmolol infusion, transition the patient to a nicardipine infusion, increase the dose of metoprolol tartrate to 100 mg twice daily, and initiate amlodipine 5 mg to maintain heart rate and blood pressure control. Table 1 details the volume of esmolol in sterile water infused and corresponding serum sodium level on each POD. After discontinuation of the infusion of esmolol in sterile water and initiation of 0.9% sodium chloride injection at 83 mL/hour (for a total volume infused of 2,600 mL), the patient's serum sodium level began to recover. On POD5, the patient was transferred to another facility for a higher level of care. No further seizures were observed on continuous electroencephalography, and all antiepileptic drugs were discontinued by POD11 with no seizure activity during the remainder of the patient's hospitalization.

KEY POINTS

- Acute hyponatremia can lead to severe neurological symptoms such as confusion, obtundation, seizures, coma, and respiratory depression, particularly with a rapid decline in serum sodium levels.
- The formulation and excipients of pharmaceutical agents should be reviewed when assessing the potential for medication-related adverse effects in complicated patient cases.
- In comprehensive patient care, patients should be regularly evaluated for iatrogenic causes of adverse events using a multidisciplinary approach.

Discussion

The esmolol product utilized at our institution is formulated in 250 mL of sterile water, which is suspected to have contributed to the hyponatremia discussed in this patient case.[2] The formulation also contains 2,500 mg of the excipient propylene glycol in each 250-mL bag, which at toxic levels is known to cause adverse effects such as anion gap metabolic acidosis, acute kidney injury, and sepsis-like syndrome.[2,3] One case report has described delirium caused by propylene glycol toxicity associated with an esmolol infusion in a pediatric patient.[4] To our knowledge, there are no other case reports regarding esmolol in sterile water and its contribution to severe hyponatremia and seizures.

Unfortunately, serum osmolarity was not measured for this patient, which, along with volume status, could have helped to determine potential causes and treatment. Therefore, causes such as postoperative hyponatremia or SIADH cannot be ruled out. Postoperative hyponatremia is typically mild and transient, with a decrease in serum sodium levels of approximately 4 mEq/L within 24 hours of surgery, and does not result in notable neurological effects.[5] The Naranjo adverse drug reaction probability scale suggested a possible relationship (score of 3) between the esmolol infusion and severe hyponatremia.[6] While other causes are unable to be ruled out, it is possible that the effect of postoperative hyponatremia was augmented by the

Table 1. Trend in Serum Sodium Levels Corresponding to Volume of Esmolol in Sterile Water Received

POD	Serum sodium level, mEq/L	Esmolol in sterile water received, mL
0	139	470
1	140	2,798
2	131	3,804
3	125	834
4	135	0
5	141	0

Abbreviation: POD, postoperative day.

use of an esmolol infusion in free water to produce the significant decrease in serum sodium levels that resulted in seizures in this patient. The applicability of the Naranjo score may also be limited because the reaction was not due to the drug itself but rather to the product formulation; thus, this reaction would not be expected to be a class effect of all β-blockers. Esmolol is compatible in formulation to other solutions, including Ringer's lactate, 0.9% sodium chloride injection, and 0.45% sodium chloride, and is commercially available in a premade formulation with 0.9% sodium chloride injection.[7]

Conclusion

It is important to be aware of the formulation and excipients of medications and their potential for adverse effects on patients. Pharmacists play a critical role in evaluating patients for adverse effects with iatrogenic causes, as described in this case report, and can provide education and insight to the medical team.

Data availability

The data underlying this article are available in the article.

Disclosures

The authors have declared no potential conflicts of interest.

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