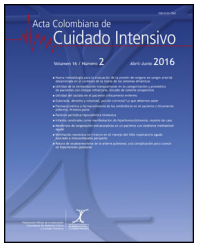
Acta Colombiana de Cuidado Intensivo xxx (xxxx) xxx–xxx

Asociación Colombiana de Medicina Crítica y Cuidado Intensivo

Acta Colombiana de Cuidado Intensivo

www.elsevier.es/acci



CASE REPORT

The enigma of hypernatremia: Ampicillin/sulbactam as an unexpected cause—A case report

Javier Polo Díaz[a,b,*], **Paola Blanco Pertuz**[c], **Luis Carbonell Riquett**[c], **Diemer Muñoz Verbel**[d], **Amilkar Almanza Hurtado**[a,b], **Carmelo Dueñas Castell**[a,b,c], **Wilfrido Coronell Rodríguez**[a,b]

[a] *Grupo de Investigación en Cuidados Intensivos y Obstetricia (GRICIO), Universidad de Cartagena, Colombia*
[b] *Gestión Salud IPS, Cartagena, Colombia*
[c] *Medicina Interna, Universidad de Cartagena, Cartagena, Colombia*
[d] *GINUMED Research Group, Corporación Universitaria Rafael Núñez, Cartagena, Colombia*

Received 21 August 2023; accepted 26 December 2023

KEYWORDS
Hypernatremia;
Ampicillin/sulbactam;
Sodium;
Acinetobacter baumannii

Abstract Pharmacological hypernatremia is a common electrolyte disorder observed in hospital settings. However, its association with antimicrobial agents remains under investigation. To the best of our knowledge, there are no documented cases of hypernatremia resulting from the use of ampicillin/sulbactam. We present the case of a 58-year-old male who developed this electrolyte imbalance during hospitalization, which was refractory to conventional management. The patient only exhibited significant clinical improvement upon modification and discontinuation of the antibiotic, thereby suggesting an unusual etiology for hypernatremia.

PALABRAS CLAVE
Hipernatremia;
Ampicilina/sulbactam;
Sodio;
Acinetobacter baumannii

El enigma de la hipernatremia: ampicilina/sulbactam como causa inesperada. Un informe de caso

Resumen La hipernatremia farmacológica es un trastorno electrolítico común en entornos hospitalarios. Sin embargo, su asociación con agentes antimicrobianos sigue siendo investigada de manera insuficiente. Hasta donde llega nuestro conocimiento, no hay casos documentados de esta entidad resultante del uso de ampicilina/sulbactam. Presentamos el caso de un hombre de 58 años que desarrolló este desequilibrio electrolítico durante su hospitalización, el

* Corresponding author.
E-mail address: javierpolod@gmail.com (J. Polo Díaz).

https://doi.org/10.1016/j.acci.2023.12.005

Please cite this article as: J. Polo Díaz, P. Blanco Pertuz, L. Carbonell Riquett et al., The enigma of hypernatremia: Ampicillin/sulbactam as an unexpected cause—A case report, Acta Colombiana de Cuidado Intensivo, https://doi.org/10.1016/j.acci.2023.12.005

cual fue refractario al manejo convencional. El paciente solo mostró una mejora clínica significativa al modificar y suspender el antibiótico, lo que sugiere una etiología inusual para este padecimiento.

Background

Hypernatremia, a hydroelectrolytic disorder characterized by a serum sodium concentration greater than 145 mEq/L, exhibits variable prevalence. Thus, while in emergencies, it ranges between 0.2% and 1%, in hospitalized patients, it fluctuates between 0.5% and 5.0%, and in critically ill patients, it can be up to ten times higher, from 2% to 6%. However, in the intensive care unit (ICU), it can reach up to 10%.[1] Hypernatremia is associated with a 40% increase in the risk of mortality and a 28% increase in the duration of ICU stay.[2]

Evidence identifies water loss as the leading cause of hypernatremia. It can be secondary to sodium gain in the hospital setting by using 0.9% isotonic saline solution.[2] In 1968, Brunner and Frick reported the first case of pharmacological hypernatremia associated with excessive administration of sodium penicillin.[3] A systematic review documented that cefuroxime, cephalothin, and ticarcillin/clavulanate are the antimicrobials most likely to cause electrolytic disorders or acid–base alterations.[4] According to the guidelines of the Infectious Diseases Society of America (IDSA), ampicillin–sulbactam, at a dose of 27 grams, is recommended as the first-line treatment for septic shock caused by *Acinetobacter baumannii*.[6] Despite evidence-based recommendations for these doses, no reports link their use with hypernatremia.[5]

We present below the case of a patient with hypernatremia associated with using ampicillin/sulbactam. Given the rarity of the presentation, we detail the diagnostic and therapeutic approach undertaken as an alert and guide about this possible association. We obtained adequately completed informed consent.

Clinical case

A 58-year-old male patient was admitted due to status epilepticus. He was diagnosed with a hypertensive emergency with target organ damage to the brain due to a left frontotemporal-basal intraparenchymal hemorrhage. The patient was intubated, and anticonvulsant treatment with valproic acid was initiated. The patient developed septic shock of pulmonary origin caused by severe pneumonia throughout his clinical course. AmpC beta-lactamase-producing *A. baumannii* was isolated in blood cultures. After being evaluated by the infectious disease team, treatment with ampicillin/sulbactam at a dose of 27 g per day was initiated.

During the first 24 h after starting the antimicrobial treatment, the patient showed a progressive increase in natremia to a maximum value of 163.1 mEq/L. Physical examination indicated that the patient was euvolemic. Measurement of urinary osmolality revealed an increase associated with acute kidney injury classified as KDIGO 3. The daily monitoring of water balances reports a positive accumulated balance before, during, and after dysnatremia. Insensible losses were not quantified since they are not part of routine monitoring in the ICU. The evidence is scarce regarding the use of insensible losses as an isolated cause of hypernatremia[1]; however, it is feasible to consider that insensible losses are an essential parameter in the evaluation of electrolytes in hospital patients, which is why we will leave it as part of the limitations of the present study together with the serum osmolarity which could not be obtained either. During hospitalization, the patient did not receive HCO3 infusions, diuretics, or parenteral nutrition. No gastrointestinal alterations were documented, but fever with a maximum temperature of 38.9 °C was reported; however, it began on day 10 of the stay, not coinciding with the onset of hypernatremia but, on the contrary, maintaining adequate levels despite the fever. The evolution over time of glucometers was appropriate for the context of a critically ill patient, with isolated measurements on three occasions outside the general safety parameters, taking values between 110 mg/dl and 180 mg/dl as a reference, presenting on day five a minimum of 87 mg/dl and day 21 a maximum of 206 mg/dl. However, these isolated values near the control point would not be the etiological cause of such marked dysnatremia. As described previously, the reason for the patient's admission was status epilepticus; for this reason, it was necessary to secure the airway from day 0, maintaining adequate sodium values until day 19. Several studies have associated hypernatremia with mechanical ventilation since this can compromise the capacity for adequate water intake due to the ventilatory device, sedation, and/or alteration of the neurological status; however, studies show that this occurs between days 7 and 9 of mechanic ventilation.[7] Considering the wide time window between the start of invasive mechanical ventilation and hypernatremia, it is not believed to cause electrolyte alteration. There are also sodium alterations secondary to intracerebral bleeding. It is crucial to remember that it is more common to find a salt-losing brain, to a lesser extent, hypernatremia. The presence of intracerebral hematoma, cerebral edema, or vasospasm could lead to the destruction of the hypothalamic nuclei, with the consequent reduction of antidiuretic hormone secretion and the development of hypernatremia; however, in this case, this patient had a normal urinary density (1.025), normal random urinary sodium (40 mmol) and

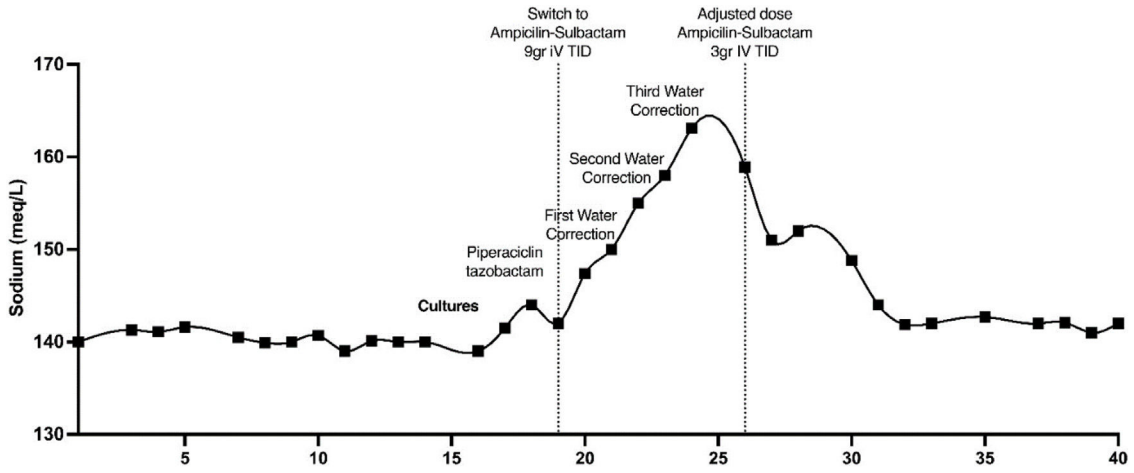


Figure 1 Changes in sodium levels over time. TID: three times a day.

a normal diuresis before the sodium imbalance, presenting a peak of maximum urinary excretion of 1.56 cc/kg/h on the 5th day of hypernatremia, normalizing on the 8th day of imbalance with a urine output of 0.87 cc/kg/h. Finally, hypernatremia related to cerebral hemorrhage generally occurs early and not as late as in this case. No other associated factors were identified.

To correct hypernatremia, we calculated the water deficit using the formula proposed by Adrogué-Madías,[5] and water replacement was initiated orally, but it did not decrease sodium levels. Consequently, it was decided to split the calculated deficit, indicating half of the input through free water and the remaining with 5% dextrose. However, sodium levels continued to rise. After correctly calculating the correction for hypernatremia and not achieving its reduction, the calculation suggested by Yun et al.[1] was applied to correct chronic hypernatremia, which involves administering 5% dextrose at 1.35 ml/kg/h. Nevertheless, we did not achieve the expected reduction in natremia.

A medical board was convened with the participation of the Internal Medicine, Critical Care, and Infectious Diseases services. The committee considered the possibility of a temporal association between initiating antibiotic treatment and developing hypernatremia. Based on this hypothesis, the dose of ampicillin/sulbactam was reduced to 12 g per day for the remainder of the 10-day treatment. Sodium levels decreased 24 h after this dose modification and normalized within 96 h (see Fig. 1).

Subsequently, there were no new episodes of hypernatremia or other electrolytic disorders, and 28 days later, the patient was transferred to a chronic care center.

Discussion

Since hypernatremia reflects a water balance disorder, its presence should trigger a diagnostic approach to define the appropriate treatment. For this, conducting a complete clinical history and physical examination is essential, emphasizing identifying predisposing factors and sources of water loss. Hypernatremia in the ICU is an electrolytic disorder that occurs in 4–26% of patients and is caused by the infusion of large amounts of isotonic fluids, high insensible losses, and inability to respond to thirst or the administration of intravenous medication. It is associated with an increased ICU stay and is configured as an independent predictor of mortality, even with relatively low levels.[8]

In our case, the patient had started treatment with ampicillin/sulbactam 24 h before the onset of hypernatremia. The doses were recommended according to the IDSA guidelines to treat cases of *A. baumannii* bacteremia in hemodynamically unstable patients.[6] Despite starting the appropriate treatment, hypernatremia was not corrected. The sodium content of a 1.5-g vial of ampicillin/sulbactam is approximately 115 mg (5 mEq). Considering that the patient received 27 g of this antibiotic daily, the total daily administered sodium amounted to 2070 mg (90 mEq).[4]

The literature does not describe cases of hypernatremia associated with ampicillin/sulbactam. This lack of evidence may be due to underdiagnosis and the fact that the doses recommended for most infections are lower than those indicated for treating *A. baumannii* bacteremia. The correlation between the start of treatment, the development of hypernatremia, and the subsequent normalization of sodium upon reducing the dose leads us to postulate this association. This case report will help healthcare professionals consider that, depending on the amounts used and the clinical context, and after ruling out secondary causes, this antibiotic could generate hypernatremia and establish appropriate treatment.

Within the limitations of this case report, we could not assess the patient's perspective, as he had a severe neurological deficit generated by the initial cerebral event. Therefore, it was impossible to establish neurological alterations that could have been derived from the hypernatremia, nor was it possible to evaluate the clinical and paraclinical improvements that could be generated from the correction of the disorder.

Ethics committee approval

The authors declare that before initiating this project, it was subjected to rigorous evaluation by the local hospital's Ethics Committee.

Removal of identifying information

Sensitive data and identifying information were removed from the study to protect the patient's confidentiality.

Conflict of interest

All authors declare that they have not received financial support from any organization for the submitted work. Moreover, they declare that they have not had associations with any organization interested in the published work in the present or the last three years. Last, they ensure no other relationships or activities could have influenced the submitted work.

References

1. Yun G, Baek SH, Kim S. Evaluation and management of hypernatremia in adults: clinical perspectives. Korean J Intern Med. 2023;38:290–302.
2. Chand R, Chand R, Goldfarb DS. Hypernatremia in the intensive care unit. Curr Opin Nephrol Hypertens. 2022;31:199–204.
3. Brunner FP, Frick PG. Hypokalaemia, metabolic alkalosis, and hypernatraemia due to ''massive'' sodium penicillin therapy. BMJ. 1968;4:550–2.
4. Kim YW. Antimicrobial-induced electrolyte and acid–base disturbances. Electrolyte Blood Press. 2007;5:111.
5. Adrogué HJ, Madias NE. Aiding fluid prescription for the dysnatremias. Intensive Care Med. 1997;23:309–16.
6. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of america guidance on the treatment of AmpC β-lactamase-producing enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* infections. Clin Infect Dis. 2022;74:2089–114.
7. Waite MD, Fuhrman SA, Badawi O, Zuckerman IH, Franey CS. Intensive care unit – acquired hypernatremia is an independent predictor of increased mortality and length of stay. J Crit Care. 2013;28:405–12.
8. Olsen MH, Møller M, Romano S, Andersson J, Mlodzinski E, Raines NH, et al. Association between ICU-acquired hypernatremia and in-hospital mortality: data from the medical information mart for intensive care III and the electronic ICU collaborative research database. Crit Care Explor. 2020;2:e0304.