



## SCIENTIFIC LETTER

## Hypernatremia and renal dysfunction after sevoflurane sedation in the intensive care unit: Three case reports

### Hipernatremia y disfunción renal tras sedación con sevoflurano en la unidad de cuidados intensivos. Reporte de tres casos

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Sedation is an essential treatment for the management of critically ill patients. Although historically sedation in ICU has been administered through the infusion of intravenous drugs, the experience of recent years has shown that the use of sedative gases can provide benefits over conventional therapy.

Sevoflurane is approved for the induction and maintenance of general anaesthesia during surgical procedures. Since the COVID-19 pandemic, its use rapidly expanded, leading to its off-label use beyond traditional surgical settings and into intensive care environments as a promising approach to address various sedation needs. It has a faster onset of action and a faster elimination, mainly through the lungs, avoiding unwanted effects such as over sedation and delay in the patients awakening.<sup>1</sup> The main reported adverse reactions of Sevoflurane are hypothermia, drowsi-

ness and fever, and less frequently is nephrotoxicity, mainly diabetes insipidus.<sup>2,3</sup> To our knowledge, there is little data describing cases with hypernatremia and renal dysfunction.

We report three cases with hypernatremia and renal dysfunction related to sevoflurane. Doses were monitored by Minimum Alveolar Concentration (MAC) and Fet% and sedation levels were monitored by Bispectral Index System (BIS). All cases were reported to the Spanish Pharmacovigilance System (Table 1, Fig. 1).

### Case 1

A 75-year-old man with a history of hypertension, sinus tachyarrhythmia and benign prostatic hyperplasia was admitted to the ICU for bilateral Sars-Cov2 pneumonia requiring orotracheal intubation. Inhaled sedation with sevoflurane was started and afterwards progressive hyperosmolar hypernatremia and renal dysfunction were observed (normal before starting sevoflurane), with values of up to 154.1 mmol/L sodium, 112 mg/dL urea, and 1.3 mg/dL creatinine. The inhaled sedation was withdrawn after 5 days of treatment

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**Table 1** Summary of case characteristics.

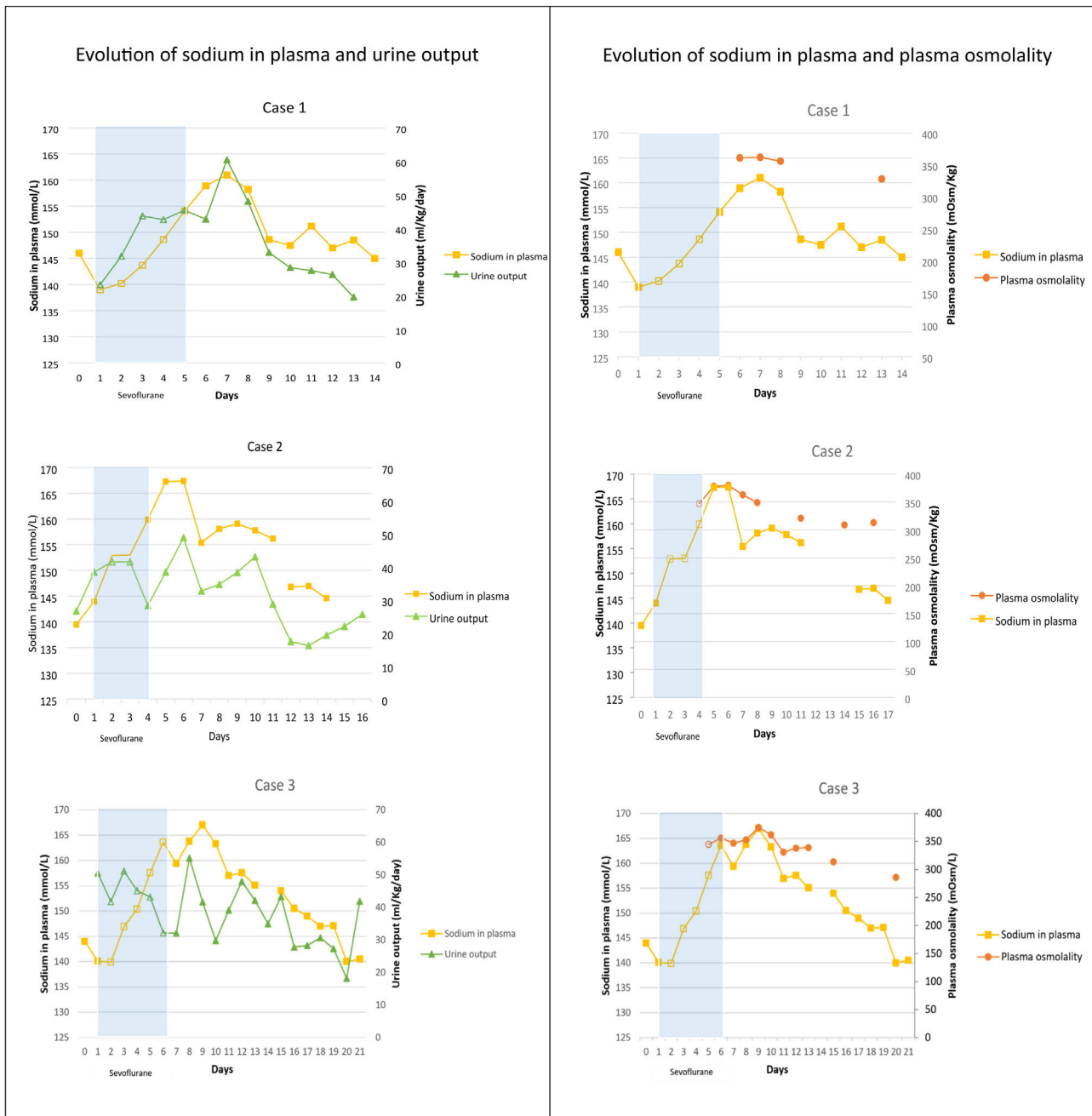
Case	Age (years)	Sex	Duration of treatment (days)	Concentration of sevoflurane in exhaled air (vol%)	BIS index range	Diuresis during treatment (ml/Kg/day)	Latency period of hypernatremia (days)	Maximum hypernatremia (mmol/L)	Blood osmolality (mOsm/Kg)	Urinary osmolality <sup>a</sup> (mOsm/Kg)	Glomerular filtrate (ml/min/1.73 m <sup>2</sup> )	Concomitant drug-induced hypernatremia	Nephrotoxic drugs with consistent temporal sequence	Treatment received	Outcome
1	75	Man	5	0.49	34–53	37.4	4	161 At 4 days after sevoflurane withdrawal	388	361 Desmopressin test with no changes in osmolality	52 6 days after starting sevoflurane	None	None	Hydrochlorothiazide fluid therapy	Recovered
2	34	Man	4	0.89	29–43	37	2	167.4 At 2 days after sevoflurane withdrawal	347	397 <sup>b</sup>	60 4 days after starting sevoflurane	None	Dexketoprofen	Hydrochlorothiazide fluid therapy, RRT	Recovered
3	24	Man	6	1.23	27–54	44	3	167 At 3 days after treatment sevoflurane withdrawal	356	373 <sup>b</sup> Desmopressin test with no changes in osmolality	63 7 days after starting sevoflurane	Ceftazidime-avibactam	None	Hydrochlorothiazide fluid therapy, RRT	Recovered

BIS: bispectral index system, CKD-EPI eGFR: glomerular filtration rate estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), RRT: Renal Replacement Therapy.

**Normal reference values:** blood sodium: 135–145 mmol/L, blood osmolality: 275–295 mOsm/Kg, urinary osmolality: 50–1200 mOsm/Kg, glomerular filtrate >90 ml/min/1.73 m<sup>2</sup>.

<sup>a</sup> In diabetes insipidus, the diagnostic criterion for osmolality is < 300 mOsm/Kg.

<sup>b</sup> Unreliable value in patients undergoing treatment with furosemide.



**Figure 1** Evolution of sodium in plasma, plasma osmolality and urine output (three cases).

due to a suspected adverse effect. During the following 24–48 h the hypernatremia and renal function worsened and later improved. The patient was fully recovered.

## Case 2

A 34-year-old man with a history of hypertriglyceridemia and previous admissions for acute pancreatitis was admitted to the ICU due to multi-organ dysfunction due to severe acute hypertriglyceridemic pancreatitis requiring orotracheal intubation. During sedation treatment with inhaled sevoflurane, progressive hyperosmolar hypernatremia was observed together with renal dysfunction (normal before

starting sevoflurane) with values up to 159.9 mmol/L sodium, 128 mg/dL urea, and 1.49 mg/dL creatinine. The inhaled sedation was withdrawn after 4 days due to a suspected adverse effect, and 48 h later hypernatremia and renal dysfunction worsened requiring continuous renal replacement therapy (CRRT). The patient was fully recovered.

## Case 3

A 24-year-old man with a history of burns due to deflagration with upper respiratory tract involvement, was admitted to the ICU for postoperative tracheal prosthesis replacement.

During sedation treatment with inhaled sevoflurane, he presented hypernatremia with plasma sodium up to 164 mmol/L and acute renal failure with urea level up to 191 mg/dL, and creatinine of 1.54 mg/dL, and hyperosmolar hypernatremia with plasma sodium up to 164 mmol/L. The inhaled sedation was withdrawn after 4 days due to a suspected adverse effect. During the following 24 h hypernatremia and renal failure worsened requiring CRRT. The patient was fully recovered.

The three reported cases of hypernatremia with hyperosmolality and renal dysfunction were men admitted to ICU for medical conditions and treated with sevoflurane for sedation between 4–6 days, with a latency period for the ADR of 2–4 days, and all fully recovered after drug withdrawal. Renal function prior to starting sevoflurane was normal in all patients and deteriorated at days 4–7 of treatment with sevoflurane, two patients requiring CRRT. Although the initial suspicion for these patients was diabetes insipidus, none of them met the full criteria for this diagnosis. The urinary osmolality was >300 mOsm/kg in all patients, desmopressin testing was only performed in two patients; and urinary osmolality was not measured in any patient. The concentration of sevoflurane in expired air was 0,49 – 1,23 vol %. Finally, it should be noted that other causes of renal dysfunction, such as hemodynamic instability, dehydration, sepsis, or nephrotoxic drugs that could cause this alteration, were ruled out. On the other hand, the hypernatremia would not be explained by the administration of hypertonic saline solution or diuretics in none of the three cases.

Nephrotoxicity related to sevoflurane has been described as renal dysfunction, mainly diabetes insipidus or polyuria, suggesting that prolonged duration of medication and high end-tidal concentrations of sevoflurane could be associated to severity of nephrotoxicity.<sup>3–5</sup> According to a pharmacovigilance study based on disproportionality analysis in the FDA Adverse Event Reporting System (FAERS) database, 14 reports of diabetes insipidus were related to sevoflurane, from a total of 554 (2.5%).<sup>6</sup> In the WHO's pharmacovigilance database (Vigiaccess) there were 15 cases of hypernatremia and 37 of diabetes insipidus related to sevoflurane. In published cases of diabetes insipidus or hypernatremia and renal dysfunction, the onset typically occurs within 2–7 days after starting sevoflurane. Nevertheless, a recent metanalysis concluded that sevoflurane was not associated with an increased serum creatinine when used for critical care sedation for less than 72 h.<sup>7</sup> The mechanism of nephrotoxicity remains unclear and controversial. Sevoflurane may cause renal injury through toxic metabolites in renal tubular cells and can temporarily disrupt Aquaporin 2 (AQO-2) channels in collecting duct membranes, leading to reduced urine concentration.<sup>8</sup>

According to the Naranjo causality algorithm, sevoflurane is a probable cause of renal dysfunction and hypernatremia.<sup>9</sup> However, for case 3, the high sodium content of ceftazidime-avibactam could contribute to hypernatremia.

Taking into account that isoflurane is less related to renal and urinary disorders and that it has recently been authorized for use in the ICU, we decided to replace sevoflurane with isoflurane in the ICU of our centre as recommended.<sup>10</sup>

In conclusion, given that sevoflurane sedation is becoming increasingly popular, it is essential for intensive care physicians to be aware of the possibility of hypernatremia,

renal disorders and diabetes insipidus associated with this drug. Further research is needed to confirm this association. Due to its widespread off-label use and to ensure patient safety, it is important to report such cases to pharmacovigilance centres.

According to the ethical standards of our hospital, informed consent has been requested from each patient for the anonymous publication of the clinical data mentioned in the manuscript.

## CRediT authorship contribution statement

- Collection and analysis of clinical information: Marta Bauçà-Socías, Eva Benveniste-Pérez, Dolly Andrea Caicedo.
- Writing the introduction: Eva Benveniste-Pérez.
- Writing the cases' description: Marta Bauçà-Socías.
- Writing the discussion: Dolly Andrea Caicedo.
- Spanish to English translation: Dolly Andrea Caicedo, Eva Benveniste-Pérez.
- Tables' and Figures' Edition: Dolly Andrea Caicedo.
- Bibliography: Eva Benveniste-Pérez, Dolly Andrea Caicedo, Eva Montané.
- Global revision of the manuscript: Eva Montané, Eva Benveniste-Pérez, Georgina de la Rosa-Loppacher.
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## Additional information

Marta Bauçà-Socías and Dolly Andrea Caicedo are first co-authors.

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