Complete Nephrogenic Diabetes Insipidus After Prolonged Sevoflurane Sedation: A Case Report About 3 Cases

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Volatile anesthetic agents, such as sevoflurane, are increasingly used for long-term sedation in intensive care units worldwide, with improved clinical outcomes reported in recent studies due to favorable pharmacological properties. Despite possible renal toxicity related to the production of plasma inorganic fluoride and concerns related to reversible impairment of renal concentrating abilities, renal injury associated with sevoflurane sedation has rarely been reported in the intensive care unit setting. We hereby report 3 cases of nephrogenic diabetes insipidus associated with prolonged sevoflurane sedation using the AnaConDa device and review the possible mechanisms of renal toxicity. (A&A Practice. XXX;XXX:00–00.)

Volatile anesthetic agents are becoming increasingly popular in intensive care units (ICUs) worldwide since the development of gas reflectors, such as AnaConDa (SEDANA Medical, Uppsala, Sweden), which allow their easy administration with an open-circuit ICU ventilator. Among them, sevoflurane has been compared to usual intravenous sedatives for long-term sedation in ICU in several studies, with positive results regarding safety and efficacy.[1–4] Despite initial concerns regarding renal toxicity related to the production of plasma inorganic fluoride (IF),[5] renal injury has rarely been reported in the ICU setting.[6] We hereby report 3 cases of nephrogenic diabetes insipidus (NDI) associated with prolonged sevoflurane sedation using the AnaConDa device. A written consent was obtained from the patients for this publication.

CASES DESCRIPTION

Case 1

A 27-year-old man was admitted to the ICU with sepsis due to multiple abscesses complicating a necrotizing ulcerative gingivitis. His previous medical history was unremarkable except for active smoking. In addition to antimicrobial therapy (amoxicillin–clavulanate), the patient was intubated and emergency surgical drainage of the abscesses was performed on the day of admission. Sedation was initially provided by intravenous propofol (3 mg/kg/h) and ketamine (0.5 mg/kg/h), but, due to intractable agitation, clonidine (0.5 μg/kg/h), sufentanil (10 μg/h), and midazolam (up to 100 mg/d) were successively added the following days. On day 8, due to persistent agitation, sevoflurane with the AnaConDa device was introduced and was then continued for 13 days. Intravenous sedatives were discontinued, except for low-dose clonidine (0.25 μg/kg/h). Sevoflurane end-tidal concentration of 1% vol and injection rate of 6–10 mL/h were used to achieve a score of −2 to 0 on the Richmond Agitation Sedation Scale ("0" refers to a calm and alert patient who spontaneously pays attention to his caregivers, whereas "−2" reflects light sedation in a patient who briefly awakens with eye contact in response to voice). Evolution of urine osmolality, plasma osmolality, urine output, and plasma sodium is displayed in Figure 1. After sevoflurane initiation, a progressive increase in urine output was noted (up to 5.6 L/d on day 17). It was accompanied by an increase in plasma sodium and plasma osmolality (144 mmol/L and 313 mOsm/kg on day 17, respectively) and a decrease in urine osmolality (252 mOsm/kg on day 17), suggesting the diagnosis of diabetes insipidus (DI). Renal function remained unchanged (creatinine clearance, 143 mL/min). Fluid administration was increased to compensate for excess fluid losses, and a therapeutic challenge with intravenous desmopressin (4 μg) was performed. Desmopressin had no significant effect on urine osmolality (235 vs 218 mOsm/kg) or on urine output (3200 vs 3490 mL/24 h) and was rapidly discontinued. The lack of improvement under desmopressin indicated complete NDI. Besides, serum arginine vasopressin (AVP) concentration was measured at 3.0 ng/mL on day 21, within the normal range (0.5–14 ng/mL). Other causes of NDI were carefully excluded, and the review of medications suggested the role of sevoflurane, which was stopped on day 21. Urine osmolality remained low, while urine output remained high over the next 7 days, and normal values were not reached until day 29. The patient was discharged from ICU on day 40 and ultimately fully recovered.

Case 2

A 43-year-old man was admitted to our ICU with acute hypoxemic respiratory failure due to influenza A pneumonia requiring intubation and mechanical ventilation. His medical history was unremarkable except for active smoking. In addition to antiviral treatment with oseltamivir,

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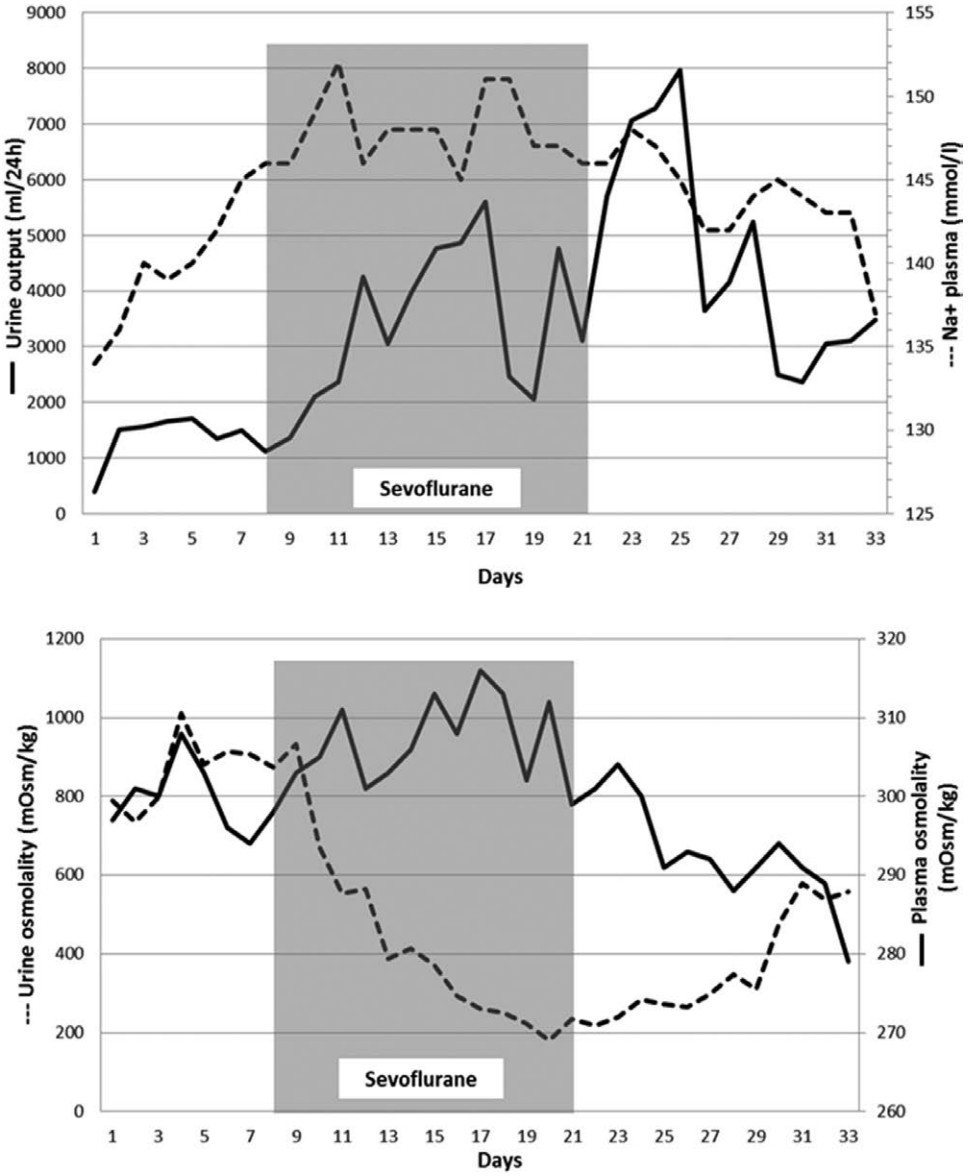

Figure 1. Evolution of urine output and plasma sodium concentration (upper panel), and of urinary and plasma osmolality (lower panel) during ICU stay in case 1. ICU indicates intensive care unit.

intravenous sedation with propofol (3 mg/kg/h), ketamine (0.4 mg/kg/h), and clonidine (0.5 μg/kg/h) was started. However, the patient became increasingly agitated, and sufentanil (up to 15 μg/h) and midazolam (0.05 mg/kg/h) were added on day 4. On day 5, due to persistent agitation, sevoflurane with AnaConDa was introduced. Sevoflurane end-tidal concentration of 1% vol and injection rate of 10–14 mL/h were used to achieve a Richmond Agitation Sedation Scale from 0 to −2. Intravenous sedatives were discontinued, except for low-dose clonidine (0.25 μg/kg/h) and low-dose propofol (1–1.5 mg/kg/h). As shown in Figure 2, after sevoflurane initiation, an increase in urine output was noted (up to 7.2 L/d on day 17), accompanied by an increase in plasma sodium and plasma osmolality (146 mmol/L and 313 mOsm/kg on day 9, respectively) and a dramatic decrease in urine osmolality (from 871 to 246 mOsm/kg on day 9), suggesting the diagnosis of DI. In parallel, despite increased fluid administration to compensate for fluid losses, the patient developed acute renal failure (decrease in creatinine clearance from 232 mL/min on day 5 to 39 mL/min on day 10). After a careful review of medications and usual causes of DI, sevoflurane was identified as the most likely cause of DI and was therefore stopped on day 9. Again, a therapeutic challenge with intravenous desmopressin (4 μg 3 times/d from day 10 to 12) failed to show any significant improvement regarding urine osmolality (from 242 to 286 mOsm/kg) or urine output (from 7200 to 5300 mL/d), confirming the diagnosis of complete NDI. During the days immediately after sevoflurane discontinuation, inappropriate polyuria persisted (>5000 mL/d), with only a slight increase of urine osmolality (337 mOsm/kg on day 14), and a progressive improvement of renal function (creatinine clearance, 100 mL/min on day 14). In parallel, extubation was successfully performed on day 11. The patient was discharged from the ICU on day 14. Brain magnetic resonance imaging did not identify any pathological process involving the pituitary gland or the pituitary stalk. Urine output and urine osmolality reached normal values

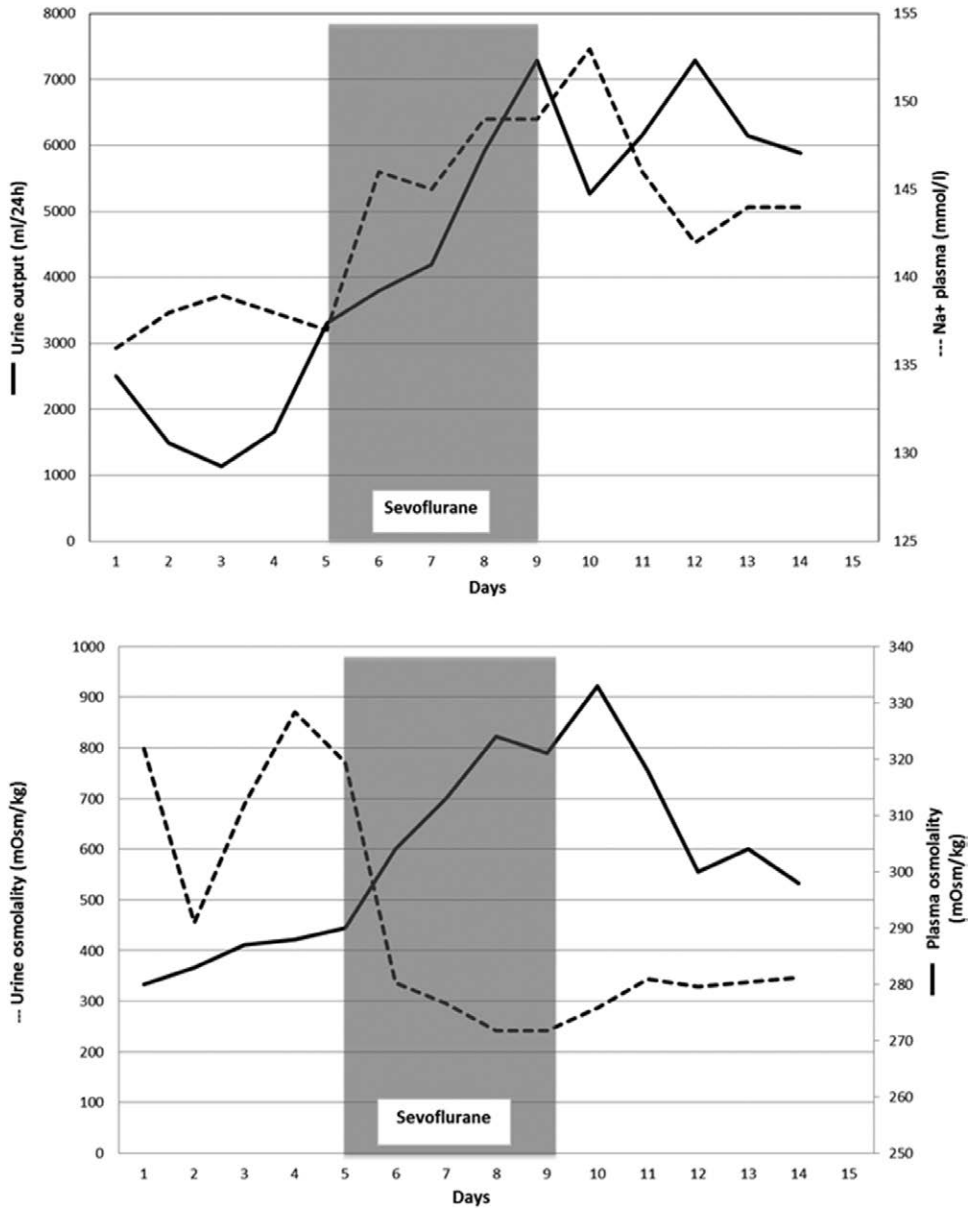

Figure 2. Evolution of urine output and plasma sodium concentration (upper panel), and of urinary and plasma osmolality (lower panel) during ICU stay in case 2. ICU indicates intensive care unit.

on day 25. The patient ultimately fully recovered and was discharged on day 29.

Case 3

A 64-year-old man was referred to the ICU for severe bronchospasm and acute respiratory failure requiring tracheal intubation and mechanical ventilation. He had a history of chronic obstructive pulmonary disease, smoking, and ethanol abuse. Sevoflurane sedation with AnaConDa device was initiated 48 hours later as bronchospasm was refractory to conventional therapy and was maintained for 6 days. As shown in Figure 3, sevoflurane administration was associated with an increase in urine output, with parallel increases in plasma sodium and plasma osmolality. Urine osmolality was not measured. Intravenous desmopressin was started on day 6, but polyuria persisted (>4 L/24 h) for several days, suggesting the diagnosis of NDI. The patient did not receive other medications associated with NDI.

DISCUSSION

Despite its extensive use in operating rooms, and, more recently, in ICUs, only a few cases of polyuria or NDI associated with sevoflurane have been described.[6–9] To our knowledge, we report the first cases of complete NDI associated with prolonged sevoflurane sedation in the ICU.

DI is characterized by the impairment of the maximal concentrating ability of the nephron associated with an inadequate AVP secretion (central DI) or an altered renal response to AVP (NDI). This clinically results in hypotonic polyuria and compensatory polydipsia. Response of <50% of urine osmolality after a therapeutic test of desmopressin administration is considered as the most accurate diagnostic test to differentiate NDI from central DI.[10] Hypotonic polyuria (urine osmolality <300 mOsm/kg and urine output >5000 mL/d) was clearly demonstrated in our 2 first patients and showed no significant response after desmopressin (12% changes in the first patient and 23% in the

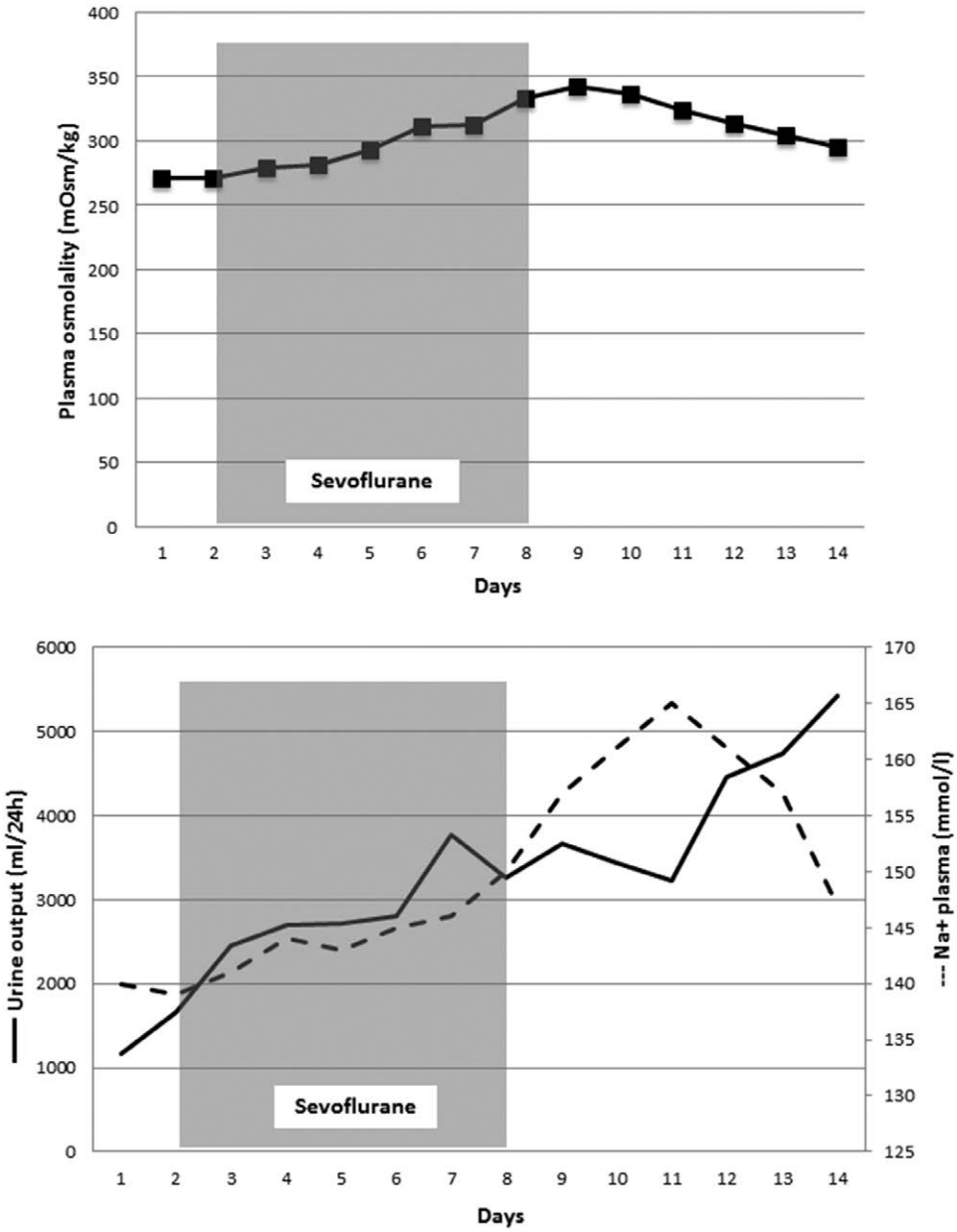

Figure 3. Evolution of urine output and plasma sodium concentration (upper panel), and of urinary and plasma osmolality (lower panel) during ICU stay in case 3. ICU indicates intensive care unit.

second patient), confirming the diagnosis of complete NDI. Urine osmolality was not measured in the third patient, but he also failed to show any improvement of polyuria under desmopressin, strongly suggesting NDI. Besides, our first patient had a serum AVP within the normal range, and the second had normal cerebral magnetic resonance imaging, both elements suggesting a nephrogenic etiology within the spectrum of DI.

None of the conditions classically responsible for NDI (electrolyte disturbances, renal infiltrative lesions, or drugs) were found in our patients, despite extensive workup. Moreover, the timing of development of hypotonic polyuria is a strong element supporting the role of sevoflurane in the genesis of NDI in our 3 patients.

Some reports suggest the association between sevoflurane and impairment of renal concentrating ability. Recently, Muyldermans et al[6] reported a case of partial NDI associated with prolonged sevoflurane sedation, while cases of transient polyuria after anesthesia with sevoflurane had been previously published.[7,8] The time to recovery for polyuria and changes in plasma and urine osmolality ranged from 3 to 14 days.[6,8] The link between sevoflurane and renal concentrating ability is probably related to aquaporin-2, an AVP-regulated water channel localized in renal collecting duct cells and involved in the regulation of water permeability. Morita et al[9] recently showed that sevoflurane induced a transient and reversible impairment of urine concentrating capabilities through a reduced aquaporin-2 expression, despite increased AVP concentrations during general anesthesia; recovery occurred within 180 minutes.

However, the precise mechanism of renal impairment remains unknown. Interestingly, nephrotoxicity related to volatile anesthetics has been linked to production of IF through hepatic cytochrome P450–mediated metabolism.[5,11]

Cytochrome P450 2E1 is predominantly responsible for sevoflurane metabolism in vivo, producing IF and hexafluoroisopropanol (HFIP).[12] Because cytochrome P450 2E1 is known to be induced by nicotine,[13] smokers could be exposed to higher levels of IF and HFIP and therefore could be more sensitive to renal toxicity while under treatment with sevoflurane. Interestingly, all patients reported hereby were active smokers. Unfortunately, we could not measure IF or HFIP concentrations in our patients to confirm this hypothesis.

Because long-term sedation with sevoflurane is becoming increasingly popular, intensive care physicians should be aware of the possibility of sevoflurane-associated complete NDI. ■

DISCLOSURES

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Contribution: This author helped write the manuscript.
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Contribution: This author helped write the manuscript.
This manuscript was handled by: Mark C. Phillips, MD.

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