Polyuria With Sevoflurane Administration: A Case Report

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Polyuria has been reported as a side effect of sevoflurane administration, but because of its relative rarity, many practitioners are not aware of this potential phenomenon. Polyuria in its extreme form can cause undesirable hemodynamic changes. A case study, in an 18-year-old man, is presented highlighting polyuria as a probable side effect of sevoflurane administration.

Keywords: Aquaporin-2, diabetes insipidus, polyuria, sevoflurane, vasopressin.

Sevoflurane was introduced in Japan in 1990, and its use quickly spread to the United States because of its low solubility in blood and tissue allowing rapid recovery and the absence of pungency.[1] However, sevoflurane has been implicated in renal injury almost since its release. Two areas of concern have historically been reported in the literature: (1) the production of compound A upon exposure to soda lime or barium hydroxide lime products and (2) the breakdown of sevoflurane into inorganic fluoride ions, which are toxic to renal cells.[1,2]

Sevoflurane has been implicated in the damage to renal cells because of the potential for its degradation by carbon dioxide absorbents to a vinyl ether called compound A. A study in 1992 found that high concentrations of compound A caused renal injury and death in rats.[1] Debate about the nephrotoxic potential of compound A in humans has persisted since that study. This phenomenon has been studied under various conditions, with the general consensus being that compound A-related renal injury is not clinically relevant with flow rates greater than or equal to 2 L/min.[1]

Sevoflurane is one of the more highly metabolized inhalation anesthetic agents in use today. Approximately 5% is metabolized by the liver, releasing inorganic fluoride ion for renal excretion. This inorganic fluoride at sufficiently high levels may produce renal dysfunction, including polyuria.[1,3,4] Multiple studies in the 1990s focused on this phenomenon using serum urea nitrogen and creatinine as markers of renal injury and concluded that sevoflurane did not pose a risk for clinically significant renal damage.[5] Later studies looked at more sensitive markers for renal injury such as *N*-acetyl-β-glucosaminidase (NAG) and β2-microglobulin, and found that renal injury did occur but was transient in nature and, again, not clinically significant.[4,6,7] However, several studies that looked at the effect of sevoflurane on the renal concentrating function of the kidney resulted in conflicting data.[4,6,8] Around this time, case reports of 4 patients experiencing polyuria with sevoflurane administration were reported in the Korean and Japanese literature.[1,9-11] In all reported cases the onset of polyuria was abrupt, remission was spontaneous, and most cases occurred within 1 hour of sevoflurane initiation. Otsuka et al[3] encountered a case of polyuria immediately following surgery using sevoflurane, which prompted these authors to undertake a study to further investigate the phenomenon.[12] This study, by Morita et al,[12] investigated a possible link between sevoflurane and a recently discovered water channel protein aquaporin-2 (AQP2).

This water channel protein is found in vesicles in the principal cells of the collecting ducts of the nephron. It was first identified as having a role in human water regulation in 1994.[12,13] One of the most important functions of the kidney is the regulation of bodily fluid balance by concentrating or diluting urine. This water channel protein is activated by arginine vasopressin (AVP)—also called antidiuretic hormone—to increase permeability of the collecting ducts of the nephron, thereby increasing water reabsorption into the body.[12] In response to AVP stimulation, AQP2 is translocated to the plasma membrane adjoining the collecting duct and renders the cells water permeable (Figure 1). Under normal circumstances, AVP is released from the posterior pituitary in response to an increase in serum osmolality[14] (Figure 2). In the presence of general anesthesia and surgery it is common to find an increase in AVP[12,13] (Table 1). The polyuria that has been noted with sevoflurane, therefore, is an unexpected finding. The studies completed by Otsuka et al and Morita et al identified that sevoflurane blunted the effects of AQP2, thereby impairing the water conservation action in response to the release of AVP.[12,13] This blunting of AQP2 urine concentration effect was most prominent 90 minutes after induction with sevoflurane and was indistinguishable from the control group at 180 minutes after induction.

A nephrogenic form of diabetes insipidus (DI) is induced. Diabetes insipidus is characterized by an impairment in renal concentrating ability and is classified as either central or nephrogenic in origin. Central or neuro-

genic DI is the inadequate secretion of AVP from the posterior pituitary. Nephrogenic DI is the inadequate response of the kidney to AVP. The AVP levels will be normal or even high in nephrogenic DI, but the collecting ducts do not increase their permeability to water. Hypovolemia and hypernatremia can occur rapidly without ongoing fluid replacement.[14] In DI, other than sodium, serum electrolytes generally are not affected.[14]

Polyuria has been reported as a side effect of sevoflurane administration, but many practitioners are not aware of this potential phenomenon. A case study is presented highlighting polyuria as a potential side effect of sevoflurane administration.

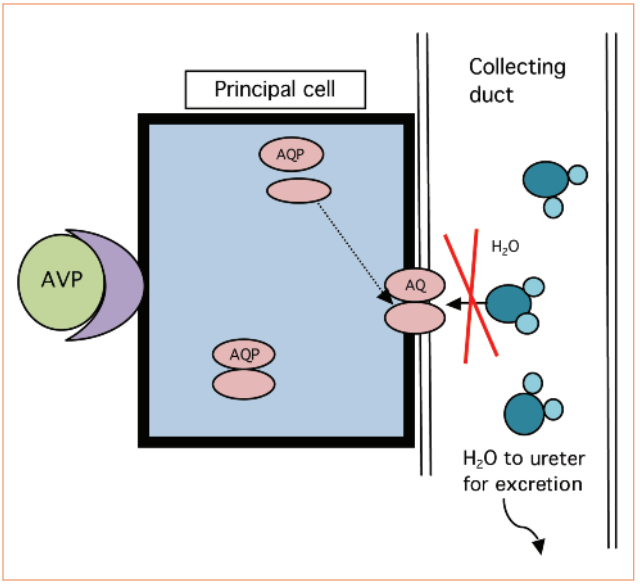

Figure 1. AQP2-Sevoflurane Interaction
When arginine vasopressin (AVP) is detected by receptors in the principal cells of the collecting duct of the nephron, aquaporin-2 (AQP2) is translocated to the wall and allows reabsorption of water (H_2O) to the body. Sevoflurane interferes with this process at the site marked by a red X.

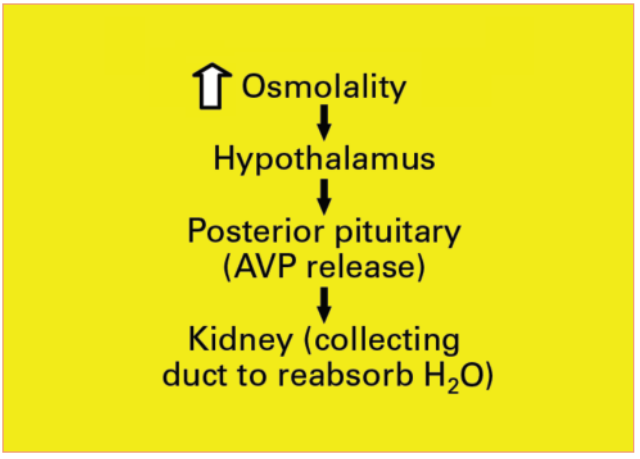

Figure 2. Kidney Response to Increased Osmolality
AVP indicates arginine vasopressin; H_2O, water.

Case Summary

An 18-year-old man was emergently admitted for gunshot wounds to the bilateral lower extremities. The right leg sustained a through-and-through wound with minimal tissue disruption. The left leg sustained an open tibia fracture with massive soft-tissue loss. The patient was taken to the operating room on day 12 for a free flap of the left latissimus dorsi to the left lower extremity. The patient was 167.6 cm tall and weighed 81.8 kg. Preoperative laboratory values were within normal limits (Table 2). Standard monitors were placed, and vital signs were within normal limits. An induction of lidocaine, 50 mg; fentanyl, 100 µg; propofol, 150 mg; and rocuronium, 50 mg, was performed, and the trachea was intubated uneventfully. Piperacillin-tazobactam (Zosyn, 3.375 mg) was given according to the patient's scheduled medications, and a warming device was placed under the patient's body. The patient was positioned in the left lateral decubitus position with the right arm in an overbody sling, and the left arm was padded at the patient's side. Maintenance anesthesia was achieved using isoflurane, and analgesia was achieved using fentanyl and morphine.

Eight hours into the case the inhalation agent was changed to sevoflurane with a flow rate of 2 L/min for ease of emergence. To this point, the patient had received 4,700 mL of lactated Ringer's solution, and 2 U peripheral red blood cells were transfused because of an estimated blood loss of 1,000 mL. Urine output was measured at 1,225 mL, for an average hourly output of 153 mL (Figure 3). A bedside hemoglobin test at this time revealed a result of 9.9 g/dL; the patient's blood pressure ranged from 88 to 100/35 to 50 mm Hg during the previous 20 minutes.

After 8.5 hours of anesthesia, care was assumed by the relieving Certified Registered Nurse Anesthetist. The blood pressure was noted to be 118/54 mm Hg, because

Decrease in mean arterial pressure
Decrease in left atrial pressure
Catecholamine release
Angiotensin II release
Atrial naturetic peptide release
Prostaglandin release
Cholinergic effects
β-Adrenergic effects
Opiates
Positive pressure ventilation
Anesthesia
Surgical stress

Table 1. Factors That Increase AVP With Anesthesia and Surgery

the patient had recently been treated with phenylephrine (Neo-Synephrine, 100 µg). The patient was also noted to have very dilute urine output. Over the subsequent hour the blood pressure continued to fluctuate: 85 to 115/40 to 52 mm Hg. Approximately 1,200 mL lactated Ringer's solution was given through a single 18-gauge peripheral intravenous (IV) catheter, and 350 µg of phenylephrine in divided doses of 50 to 100 µg were given to maintain a mean arterial pressure of 60 mm Hg. The patient also remained tachycardic with a heart rate in the range of 120/min. Urine output in the subsequent hour was noted to be 1,650 mL.

Attempts at venous access were unsuccessful, so laboratory samples were not obtained. An arterial blood gas sample with hemoglobin was obtained and revealed the following: pH, 7.44; carbon dioxide (CO_2), 36.6 mEq/L; partial pressure of oxygen (Po_2), 405.7 mm Hg; plasma bicarbonate (HCO_3^-), 24.6 mEq/L; base excess (BE), –0.5 mEq/L; arterial oxygen saturation (Sao_2), 96.8%, and hemoglobin, 7.0 g/dL. The only medications administered during the 1 hour before the onset of polyuria were sevoflurane/oxygen and phenylephrine. Sevoflurane was discontinued at this time, after approximately 1.5 minimum alveolar concentration hours of administration, and isoflurane was reinitiated at 1.2%. The urine output was 600 mL in the next 30 minutes after discontinuation of sevoflurane before becoming more concentrated in appearance (Figure 4) and then averaged 175 mL/h during the remaining 3 hours of the case. Blood pressures stabilized in the range of 120 mm Hg systolic with mean arterial pressures of approximately 70 mm Hg after an additional unit of peripheral red blood cells was given. The remainder of the case was uneventful. The patient was taken to the postanesthesia care unit, was extubated, and remained in stable condition. Postoperative laboratory values revealed a blood chemistry panel virtually unchanged from preoperative levels (see Table 2).

Discussion

Sevoflurane has been implicated in damage to renal cells because of its reaction with soda lime or barium hydroxide lime to form compound A.[1] Numerous investigators have concluded that the use of sevoflurane with flow rates greater than 2 L/min is not associated with renal compound A toxicity. Soda lime was the CO_2 absorber used in this case, and flow rates were consistently maintained at greater than 2 L/min. Compound A-related renal injury is not likely the cause of polyuria noted in this case.

Phenylephrine was chosen to mitigate the hypotension

Laboratory test	Preoperative	Postoperative
Sodium (mEq/L)	134	134
Potassium (mEq/L)	4.7	3.6
Chloride (mEq/L)	100	100
Plasma bicarbonate (mEq/L)	30	31
Serum urea nitrogen (mg/dL)	14	5
Creatinine (mg/dL)	0.67	0.56
Glucose (mg/dL)	94	Not done
Hemoglobin (g/dL)	10.6	11
Hematocrit (%)	31.6	33.1
Platelets (× 10^9/L)	573	Not done
White blood cells (× 10^9/L)	12.6	Not done
Calcium, total (mg/dL)	9.3	Not done

Table 2. Preoperative and Postoperative Laboratory Values

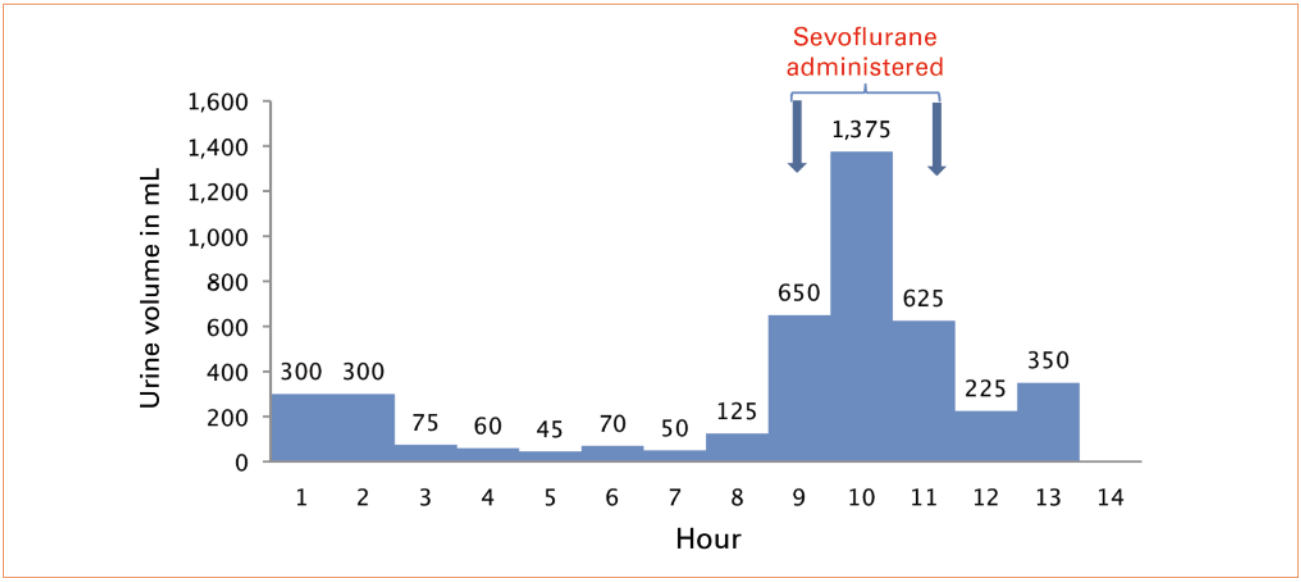

Figure 3. Hourly Urine Output Depicting Sevoflurane Administration

Figure 4. Visual Change in Urine Concentration With Sevoflurane Administration

Bottle 1 and approximately one-third of bottle 2 resulted from the first 10 hours of the operation. Two-thirds of bottle 2 and all of bottle 3 resulted from the 1-hour period of polyuria noted during sevoflurane administration. The remaining urine in bottle 4 was excreted after the sevoflurane was discontinued.

while fluids were administered and blood was obtained. Phenylephrine was chosen due to its short duration of action and its unlikeliness to worsen existing tachycardia. Vascularization of the free flap had not yet occurred, making untoward effects of vasoconstriction less of a concern. Renal effects of phenylephrine include renal vasoconstriction and a decrease in urine output, so it is not considered to be a cause of the polyuria.[15]

Nephrogenic DI induced by sevoflurane is suspected to be the cause of the polyuria observed in this case, although this cause and effect cannot be definitively concluded. Neurogenic DI is unlikely because the common causes of neurogenic DI, such as lesions of the brain (as documented by admission computed tomographic scan), head injury, infection, or known immunologic disorder, were not observed.[14] Other causes of nephrogenic DI, such as lithium toxicity, hypercalcemia, hypokalemia, or demeclocycline also can be ruled out.[14] Polyuria has also been shown to occur in response to fasting within 24 hours,[16] and since this patient had fasted for greater than 24 hours, this cannot be ruled out as a cause. The resolution of the polyuria within 40 minutes of the discontinuation of the sevoflurane, however, makes it a likely candidate for the cause of the patient's polyuria.

Polyuria associated with sevoflurane has been described as rare.[1,12] However, perhaps it is more common than originally believed as many patients do not have indwelling urinary catheters, many practitioners do not regard sevoflurane as a potential cause of polyuria, and studies suggest this phenomenon may be transient, making it difficult to identify in less extreme forms.[1,12] Clinicians should be aware of the possible occurrence of sudden-onset polyuria in the presence of sevoflurane. Although reports of this phenomenon have shown spontaneous termination of the polyuria without change in inhalation agent, the fluctuations in fluid status and hemodynamics make this an undesirable potential side effect of this widely used anesthetic gas. In this reported case the patient was young and otherwise healthy, and still required stabilization with pressors and fluids for a short duration. If the polyuria is unrecognized or occurs in a compromised, elderly, or pediatric patient, the effects of polyuria could be more pronounced.

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