HHS Public Access

Author manuscript

Ann Intern Med Clin Cases. Author manuscript; available in PMC 2022 June 30.

Published in final edited form as:

Ann Intern Med Clin Cases. 2022 ; 1: . doi:10.7326/aimcc.2022.0087.

Why So Salty? Transient Diabetes Insipidus After Discontinuation of Vasopressin

Jacqueline A. Urban, MD[1], **Francis Zirille, MD**[1], **Tyree H. Kiser, PharmD**[2], **Yael Aschner, MD**[3]

[1]Internal Medicine Residency Training Program, Division of General Internal Medicine, University of Colorado School of Medicine, Aurora, Colorado

[2]Department of Clinical Pharmacy, University of Colorado School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado

[3]Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado School of Medicine, Aurora Colorado

Abstract

In recent years, vasopressin has been increasingly used as an early treatment of vasopressor-refractory septic shock. In this article, we describe 2 episodes of transient diabetes insipidus after vasopressin for the treatment of septic shock was discontinued, which adds to a modest number of case studies reporting the same phenomenon. With the anticipated continued use of vasopressin in intensive care units, it can be expected that this adverse effect will occur with some frequency. Awareness and early recognition of this phenomenon can lead to prompt diagnosis and treatment.

Keywords

Vasopressin; Shock; Intensive care units; Case series

Background

Continuous infusion of vasopressin is increasingly used in the intensive care unit (ICU) as treatment of vasopressor-refractory distributive shock (1). The use of vasopressin as an adjunct to catecholamine vasopressor therapy has increased since publication of the Vasopressin Versus Norepinephrine Infusion in Patients With Septic Shock (VASST) trial in 2008 (2), and the most recent Surviving Sepsis guidelines recommend vasopressin as the second-line agent after norepinephrine in treating septic shock (3). Vasopressin is generally well-tolerated with minimal side effects at usual doses (0.04 IU/min or less). However, data are emerging that suggest vasopressin may cause transient diabetes insipidus

Corresponding Author: Jacqueline A. Urban, MD; jacqueline.urban@cuanschutz.edu.

Disclosures

Disclosure forms are available with the article online.

(DI) when discontinued. To date, there have been 14 case reports (4–12) describing this occurrence. With the use of vasopressin now standard in ICU practice, it is reasonable to expect further reports of this phenomenon. In this case series, we describe transient DI after discontinuation of vasopressin for the treatment of septic shock, adding to the collective body of evidence and heightening the need to improve recognition of DI after vasopressin cessation.

Objectives

- Describe an infrequently reported phenomenon that may be encountered in common clinical practice
- Review possible mechanisms of action responsible for this condition
- Suggest monitoring electrolytes closely at cessation of vasopressin infusion for timely recognition and appropriate treatment of DI

Case 1

A 77-year-old man with a medical history of epileptic seizures presented from a skilled-nursing facility for breakthrough tonic-clonic seizures. Admission laboratory values revealed hypernatremia with a serum sodium level of 152 mmol/L (normal range, 133–145 mmol/L). A computed tomography scan of the head was remarkable only for stable diffuse volume loss. Hypernatremia was attributed to hypovolemia from poor oral intake and appropriately corrected with volume resuscitation. Tonic-clonic seizures resolved, but on hospital day (HD) 5, continuous electroencephalogram revealed subclinical focal status epilepticus. Subclinical seizures persisted for 2 weeks despite an aggressive antiepileptic drug regimen. On HD 38, the patient was transferred to the medical ICU with hypotension progressing to shock requiring norepinephrine infusion. Broad-spectrum antibiotics were initiated for presumed septic shock from aspiration pneumonia, though the cause was never confirmed with positive culture data. On HD 39, the patient required intubation for acute hypoxic respiratory failure. Hypotension worsened in the peri-intubation period, with mean arterial pressure below 65. Norepinephrine was titrated to a rate of 0.25 mcg/kg/min. Given this high norepinephrine requirement, vasopressin was initiated at a nontitrated rate of 0.04 IU/min, which decreased the norepinephrine infusion to more favorable rates. The vasopressin infusion continued for 4 days and the patient was able to be weaned off all vasopressors on HD 43. Prior to, and for the duration of the vasopressin infusion, the patient's sodium level remained stable in the 140 mmol/L range. On the morning of HD 44, routine laboratory values revealed a sodium level of 160 mmol/L. This corresponded with a 24-hour urine output (UOP) greater than 6 L. Subsequent laboratory analysis revealed a measured serum osmolality of 321 mOsm/kg (normal range, 275–305 mOsm/kg), and a relatively low urine osmolality (Uosm) of 243 mOsm/kg (normal range, 50–1400 mOsm/kg). The patient was diagnosed with DI and a nephrology consultation was requested. The patient was started on DDAVP at 2 mcg intravenously every 6 hours, which resulted in successful correction of his sodium and normalization of UOP over the subsequent 48 hours (Figure 1). The Uosm increased to 560 mOsm/kg over the first 24 hours of DDAVP administration. The patient continued to receive DDAVP over the next 3 days, which resulted in a brief overcorrection

of the serum sodium to a nadir of 129 mmol/L on HD 47. At that time, DDAVP was discontinued and the patient received a bolus 150 mL of 3% saline solution, followed by 0.9% saline at a rate of 100 mL/h for 24 hours. This resulted in large-volume UOP and correction of serum sodium to 135 mmol/L by HD 48. From this point forward, the patient self-maintained a normal serum sodium level without requiring further medical or pharmacologic interventions. Given the transient nature of the electrolyte abnormalities, a magnetic resonance imaging scan was not pursued because of the patient seemingly regaining normal pituitary function.

Case 2

A 40-year-old woman with history of type 2 diabetes mellitus, opioid use disorder in remission, pancreatis divisum status post Whipple procedure, and recent history of recurrent episodes of acute hypoxic respiratory failure from cryptogenic organizing pneumonia (COP) was transferred from an outside hospital with respiratory failure from acute respiratory distress syndrome. Given her prior diagnosis of COP, she was treated with high-dose methylprednisolone at 125 mg every 6 hours. Respiratory cultures grew methicillin-susceptible *Staphylococcus aureus* and urine cultures grew *Escherichia coli*. Despite appropriate antimicrobial treatment with cefazolin, she required venovenous extracorporeal membrane oxygenation (VV-ECMO) on HD 7 for refractory hypoxemia. On HD 10, the patient had a tracheostomy placed because of a failure to extubate, and on HD 12 she had improved enough for decannulation from VV-ECMO. By HD 21, she no longer required ventilatory support, and steroids were progressively tapered from methylprednisolone to prednisone 80 mg daily. She was transferred out of the ICU on HD 28. On HD 36, the patient decompensated, requiring reintubation. Empiric vancomycin and cefepime were initiated and the steroid dose increased again to methylprednisolone 250 mg every 6 hours. Work-up, including bronchoscopy, revealed rare *E coli* and no evidence of alveolar hemorrhage. Over the subsequent 10 days, the patient required high ventilator settings and suffered recurrent aspiration events, with hypotension resulting from septic shock occurring on HD 46. At this time, she required initiation of a norepinephrine drip, with rates as high as 0.37 mcg/kg/min. Vasopressin was added at a nontitratable rate of 0.04 IU/min. Blood cultures grew *E coli* and yeast, and antibiotic coverage was adjusted to include meropenem and anidulafungin, with subsequent hemodynamic improvement. On HD 50, vasopressin was discontinued. Morning laboratory values on HD 51 revealed a serum sodium level of 145 mmol/L, a change of 21 mmol/L from the morning before. The patient's UOP was 4.9 L in the 24 hours prior, though may have been augmented by furosemide (Lasix) administration (Figure 2). Uosm at this time was 97 mOsm/kg. The patient received 2 L of dextrose 5% in water as well as 5 mcg intravenous of DDAVP. Repeat Uosm 6 hours after DDAVP administration had increased to 319 mOsm/kg. Over the following 48 hours, she received 4 L of dextrose 5% in water to maintain appropriate serum sodium; no additional DDAVP was required. The patient's UOP remained high without the use of diuretics for the next few days and then returned to normal. Once again, no head imaging was pursued because of the transient nature of this brief episode of DI.

Discussion

These cases contribute to the small but growing body of evidence demonstrating that the discontinuation of vasopressin may be associated with transient DI. Vasopressin is a synthetic analogue of antidiuretic hormone (ADH) and functions as a vasopressor through antagonism of V1 receptors on vascular smooth muscle cells, leading to vasoconstriction and antagonism of V2 receptors (V2Rs) in renal tubules, in turn leading to volume retention. Further, vasopressin increases vascular sensitivity to catecholamines, which accounts for its defined role as a second agent after norepinephrine for refractory shock (13).

The mechanism underlying the development of DI after vasopressin administration for shock remains unknown. One proposed mechanism is the downregulation of V2Rs in the renal collecting tubules in response to overstimulation by vasopressin. When V2Rs are downregulated, aquaporin-2 channel expression is reduced and the kidneys lose the ability to retain free water and concentrate the urine, resulting in polyuria of dilute urine and hypernatremia, the clinical hallmarks of DI (10). An interesting feature of this proposed mechanism is that it differs from the traditional central DI picture because it does not include a decreased ADH release or availability. Another possible mechanism might be the downregulation of ADH release by the pituitary gland from a negative feedback loop in the setting of exogenous vasopressin administration. This decrease in ADH release may temporarily cause a central DI in vulnerable individuals that responds to DDAVP while the posterior pituitary adapts to the cessation of vasopressin administration and once again begins to produce endogenous ADH.

We were able to distinguish central DI from nephrogenic DI in these cases by the robust response to DDAVP, another synthetic ADH analogue. Both patients demonstrated complete DI as defined by an increase in urine osmolality of more than 100% after DDAVP administration. This response to exogenous replacement of ADH confirmed that the condition was from decreased availability of ADH, rather than the ability of V2Rs on the renal collecting tubules to respond (Table 1). Nephrogenic DI, by definition, should not respond to DDAVP. Interestingly, all previously mentioned case studies of DI following vasopressin cessation have demonstrated a similar response to DDAVP, suggesting this phenomenon is always of the central variety. Of note, within 48 hours, neither patient continued to require DDAVP to maintain normal serum sodium levels (Figures 1 and 2) and were able to independently reconcentrate their urine. This pattern differs from the typical picture of central DI, which is generally persistent once present.

There may be underreporting of this phenomenon in the literature because of challenges in determining the cause of DI in patients with confounding neurologic comorbid conditions and/or concomitant use of offending medications (Table 1). Many of the existing case reports describe patients with previous neurologic disease or recent neurosurgical procedures. However, there is a nonsignificant number of cases, such as our second case, with no baseline neurologic defects before the event. For this reason, it is difficult to identify other risk factors besides critical illness, which will always be true of patients requiring vasopressin. It would be reasonable to assume that both patients in our series acquired some degree of anoxic brain injury given their medical circumstances, but unfortunately

neither patient had timely imaging to confirm this because the DI was transient in nature and the medical teams felt no further work-up was necessary. With the ever-increasing use of vasopressin infusion for vasopressor-refractory shock, physicians should be aware of this potential complication. Electrolytes should be closely monitored after discontinuation of vasopressin, and DI should be considered when hypernatremia develops to ensure rapid and appropriate treatment.

Funding

This study was supported by the Colorado Clinical and Translational Sciences Institute (CCTSI). The CCTSI is supported in part by Colorado CTSA Grant UL1TR002535 from NCATS/NIH. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

References

1. Sacha GL, Kiser TH, Wright GC, et al. Association between vasopressin rebranding and utilization in patients with septic shock. Crit Care Med. 2022;50:644–54. doi:10.1097/CCM.0000000000005305 [PubMed: 34605778]
2. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877–87. doi:10.1056/NEJMoa067373 [PubMed: 18305265]
3. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49:e1063–1143. doi:10.1097/CCM.0000000000005337 [PubMed: 34605781]
4. Kristeller JL, Sterns RH. Transient diabetes insipidus after discontinuation of therapeutic vasopressin. Pharmacotherapy. 2004;24:541–5. doi:10.1592/phco.24.5.541.33348 [PubMed: 15098812]
5. Ramers C, Govert JA, Clay AS. Transient acquired diabetes insipidus after vasopressin therapy for hypotension: a case report (abstract). Chest. 2005;128:454S–5S.
6. Peskey CS, Mauermann WJ, Meyer SR, et al. Vasopressin withdrawal associated with massive polyuria. J Thorac Cardiovasc Surg. 2009;138:491–2. doi:10.1016/j.jtcvs.2008.06.032 [PubMed: 19619801]
7. Bhaskar P, John J, Bin Sallehuddin A. Polyuria after cessation of vasopressin in a child after cardiac surgery. J Cardiothorac Vasc Anesth. 2014;28:e24–5. doi:10.1053/j.jvca.2014.01.014 [PubMed: 24685362]
8. Shiber JR, Johnson D. Iatrogenic central diabetes insipidus induced by vasopressin withdrawal. Open J Clin Med Case Rep. 2015;1:1042.
9. Sundar K, Biesboer A. Transient diabetes insipidus upon discontinuation of a vasopressin infusion (abstract). Crit Care Med. 2016;44:1678.
10. Bohl MA, Forseth J, Nakaji P. Transient diabetes insipidus after discontinuation of vasopressin in neurological intensive care unit patients: case series and literature review. World Neurosurg. 2017;97:479–88. doi:10.1016/j.wneu.2016.09.122 [PubMed: 27742514]
11. Rana H, Ferguson N, Dicpinigaitis PV. Diabetes insipidus after discontinuation of vasopressin infusion for septic shock. J Clin Pharm Ther. 2018;43:287–90. doi:10.1111/jcpt.12627 [PubMed: 28895166]
12. Carman N, Kay C, Petersen A, et al. Transient central diabetes insipidus after discontinuation of vasopressin. Case Rep Endocrinol. 2019:2019:4189525. doi:10.1155/2019/4189525 [PubMed: 31885944]
13. Kislitsina ON, Rich JD, Wilcox JE, et al. Shock – classification and pathophysiological principles of therapeutics. Curr Cardiol Rev. 2019;15:102–3. doi:10.2174/1573403X15666181212125024 [PubMed: 30543176]

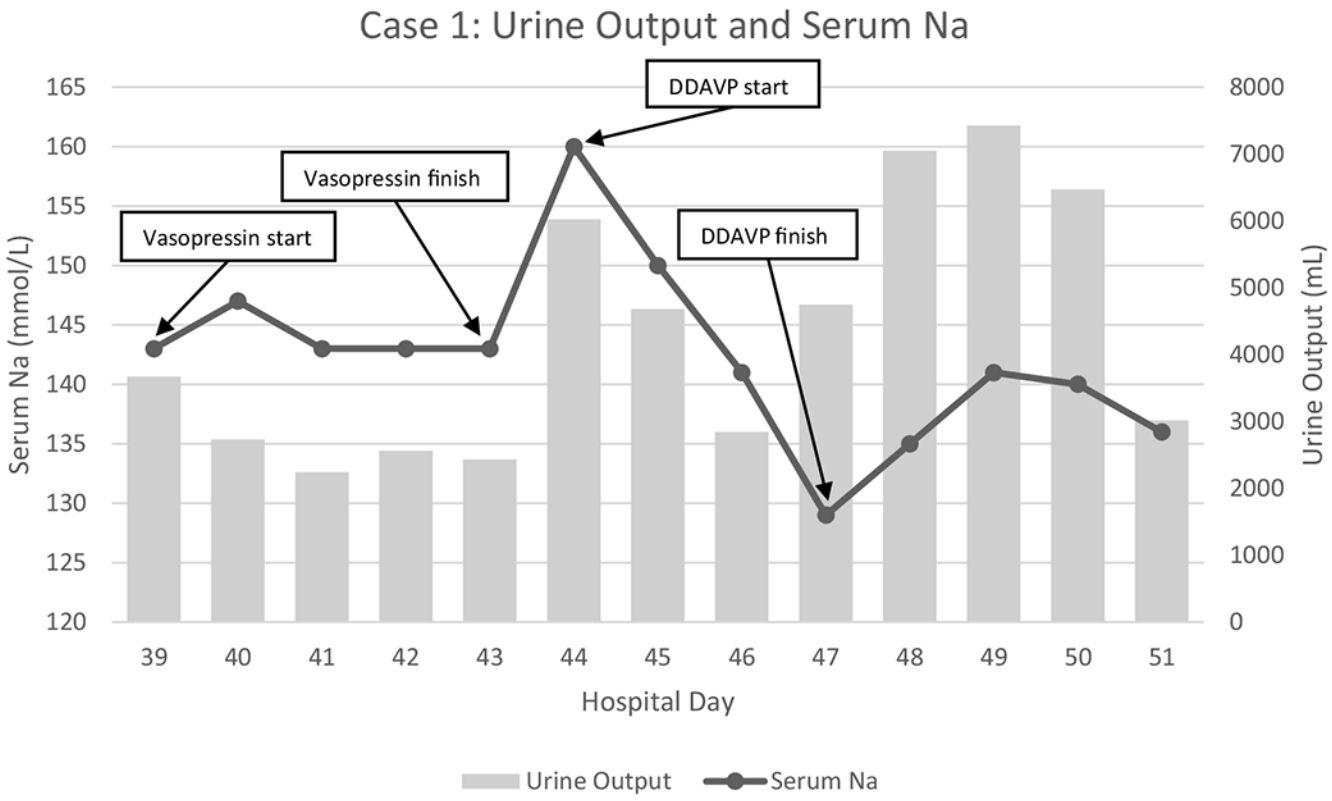

Figure 1.

Changes in serum Na and urine output with DDAVP administration in case 1. While receiving vasopressin, this patient maintained a stable serum Na level, but with the discontinuation of vasopressin, hypernatremia and large volume UOP developed, consistent with DI. DDAVP administration began on hospital day 44, followed by normalization of UOP and serum Na. DI = diabetes insipidus; Na = sodium; UOP = urine output.

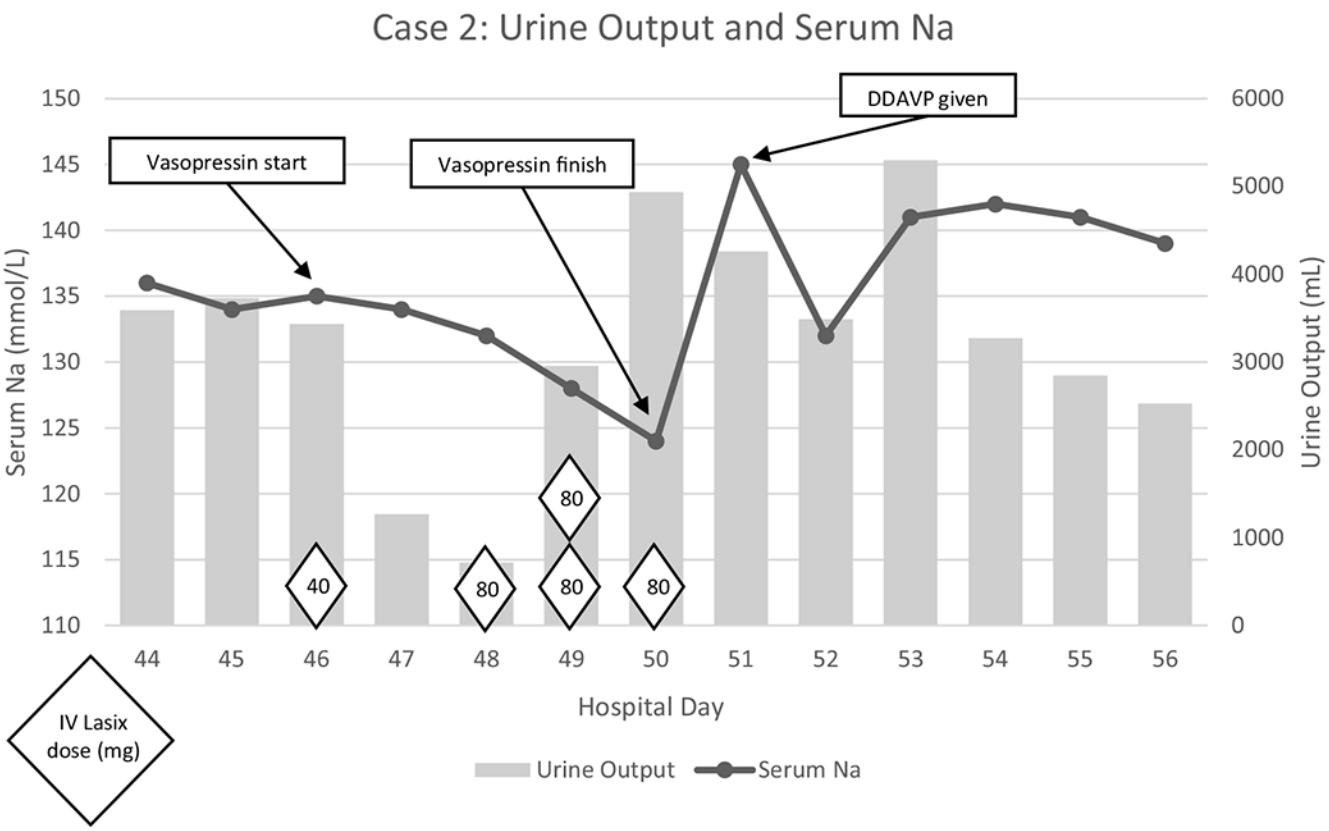

Figure 2.

Changes in serum Na and urine output with DDAVP administration in case 2. With the discontinuation of vasopressin, this patient's serum Na level increased by 21 mmol/L in the span of 24 hours with a urine output of almost 5 L. Despite the confounding factor of intravenous Lasix affecting the urine output, the degree of polyuria seen on HD 50 when vasopressin was discontinued is out of proportion to the quantity of Lasix given. DDAVP was given on HD 51, followed by normalization of UOP and serum Na. HD = hospital day; Na = sodium; UOP = urine output.

Table 1.

Differential Diagnosis of Polyuria and Defining Features

Causes	Defining Features	Laboratory Values	Causes
Osmotic diuresis	Large solute concentrations filtered by the kidney that cannot be substantially reabsorbed	• Urine osmolality >600 mOsm/kg • Total daily osmolar output >1000 mOsm *	• Glucose: hyperglycemia, SGLT2 inhibitor use • Urea: azotemia, exogenous administration, tissue catabolism • Sodium: intravenous fluid administration, relief of bilateral urinary tract obstruction • Mannitol administration
Primary polydipsia	Primary increase in water intake	• Urine osmolality >700 mOsm/kg after water restriction	• Psychiatric illness • Iatrogenic dry mouth (i.e., phenothiazines) • Hypothalamic lesions affecting the thirst center • Some infiltrative diseases (i.e., sarcoidosis)
Nephrogenic DI	Impaired response to ADH by the V2 receptors in the renal tubules Limited response to DDAVP	Complete nephrogenic DI • Increase in urine osmolality <15% AND • Urine osmolality <300 mOsm/kg after DDAVP administration Partial nephrogenic DI • Increase in urine osmolality 15%–45% AND • Urine osmolality <300 mOsm/kg after DDAVP administration	• Hereditary: mutations in V2 receptor, aquaporin-2 genes • Electrolyte derangements: hypercalcemia, hypokalemia • Kidney disease: bilateral urinary tract obstruction, SCD, ADPKD, medullary cystic kidney disease, renal amyloidosis, Sjogren syndrome • Drugs: lithium, cidofovir, foscarnet, amphotericin B, ifosfamide, ofloxacin, orlistat, didanosine • Bardet-Biedl syndrome • Bartter syndrome
Central DI	Decreased release of ADH from the posterior pituitary gland Significant response to DDAVP	Complete central DI • Increase in urine osmolality >100% after DDAVP administration Partial central DI • Increase in urine osmolality 15%–100% AND • Urine osmolality >300 mOsm/kg after DDAVP administration	• Idiopathic • Familial and congenital diseases: familial central DI, Wolfram syndrome, PCSK1 gene deficiency, congenital hypopituitarism, septo-optic dysplasia • Neurosurgery, brain tumors, trauma to the hypothalamus and posterior pituitary • Hypoxic encephalopathy • Infiltrative disorders • Langerhans cell histiocytosis • Postsupraventricular tachycardia • Anorexia nervosa

Ann Intern Med Clin Cases. Author manuscript; available in PMC 2022 June 30.

* Total daily osmolar output = urine osmolarity × 24-hour urine output.

Abbreviations: ADH = antidiuretic hormone; ADPKD = autosomal dominant polycystic kidney disease; DI = diabetes insipidus; PCSK1 = proprotein convertase subtilisin/kexin-type 1; SCD = sickle cell disease.