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A Unique Case of Dexmedetomidine (Precedex) Induced Diabetes Insipidus in the ICU and Literature Review

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Case Report
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Abstract

Background: While there have been a few cases of dexmedetomidine induced polyuria mainly in the setting of anesthesia during surgery, there have been few reports of this serious complication in the ICU. Here, we present a unique case of Precedex induced diabetes insipidus and highlight the importance of its increased awareness considering the widespread use of this medication.

Case Summary: We present a case of diabetes insipidus induced by Dexmedetomidine in the intensive care setting. The patient was admitted with acute respiratory failure requiring sedation and mechanical ventilation. The patient developed polyuria and severe hypernatremia during infusion of Precedex, the only one of its kind. The urine output decreased and the electrolyte abnormalities improved significantly after stopping the medication. A literature search was also conducted through the PubMed and SCOPUS databases with the search terms "dexmedetomidine" AND "polyuria." All found articles were included in the review, but full-texts for two were not accessible. Factors analyzed included infusion rate of dexmedetomidine, onset of diuresis relative to infusion, the setting (ICU, surgery, etc.), and other methods of sedation used in the patient's care.

Conclusion: As dexmedetomidine is used more frequently in intensive care units throughout the world, critical care physicians should become increasingly aware of this potentially severe side effect of the drug and should closely monitor urine output, osmolality and serum electrolytes while patients receive the drug.

Keywords: Anesthesia; Critical Care; Dexmedetomidine; Diabetes Insipidus; Intensive Care Unit; Polyuria

Abbreviations: ICU: Intensive Care Unit; ER: Emergency Room; BUN: Blood Urea Nitrogen; ADH: Anti-Diuretic Hormone; NDI: Nephrogenic Diabetes Insipidus

Introduction

Dexmedetomidine (brand name: Precedex) is a commonly used medication in medical intensive care units to treat delirium and to serve as an adjunctive therapeutic agent for sedation. This highly selective α2-agonist is known to cause transient hypertension after a loading dose, bradycardia, and hypotension due to its peripheral vasoconstrictive and sympatholytic properties [1]. Another theoretical side effect is suppression of arginine-vasopressin release, leading to polyuria [2]. While there have been reports of intraoperative dexmedetomidine induced polyuria especially in the setting of spine surgery in the anesthesia literature [2-5], the occurrence of central diabetes insipidus due to Precedex in the intensive care unit is more rare, and

not well documented, given the increase in usage of this drug [6-9]. Dehydration due to fluid loss and resulting electrolyte imbalances can worsen hypotension and cause further complications in already critically ill patients, including coma and death. Although rare, this potentially severe side effect of dexmedetomidine warrants further evaluation and heightened awareness among critical care physicians. Here, we present a unique case of dexmedetomidine induced diabetes insipidus in the ICU.

Case Report

Currently, the patient is admitted at a long term acute care hospital with a tracheostomy. Patient cannot verbalize or write. The corresponding author spoke to the patient's wife in presence of a witness and received consent to use patient's information for the case report.

A 66-year-old Caucasian male with a past medical history of severe chronic obstructive pulmonary disease, bronchiectasis, and acute renal failure presented to the ER complaining of fever, cough, and shortness of breath. His saturations continued to deteriorate, and he was intubated and admitted to the ICU for acute hypercapnic hypoxemic respiratory failure requiring mechanical ventilation. The patient was hemodynamically unstable, in septic shock, and sedated with propofol and fentanyl at this time. He was treated with broad spectrum antibiotics including azithromycin, Fortaz and vancomycin. Sodium level at the time of admission was 147mEq/L. Kidney function was stable with an average urine output of 2.5-3 liters for the first two days of hospitalization. He underwent a fiberoptic bronchoscopy the following morning. The next day, the patient's respiratory rate increased to more than 40, and it was determined that the current method of sedation was not being tolerated. Propofol was discontinued and Precedex was started at a rate of 0.5mcg/kg/hr. Immediately during the dexmedetomidine infusion, the patient developed abrupt onset polyuria and diuresed 9.8 liters of fluid with sodium levels peaking at 181mEq/L that same day. Urine osmolality was 382mOsm/kg H_2O and serum osmolality was 388mOsm/kg. He was immediately taken off the Precedex and switched back to propofol with an IV infusion of dextrose 5% in water. The nephrology service was consulted for severe hypernatremia. Over the next few days after the dexmedetomidine had been discontinued, the sodium level did fall to 152mEq/L and fluid infusion was continued. However, the patient was unable to be weaned off ventilation, and it was determined by the medical team that the patient would benefit from a tracheostomy and a PEG tube.

At first, the cause for the polyuria was not evident. The patient's home medications at the time of admission included Tylenol, DuoNeb, an Anoro inhaler, and multivitamins. In the hospital, he was also receiving Levophed, propofol, azithromycin, ceftazidime, famotidine, heparin, lorazepam, morphine, and vancomycin. A CT scan of the head was conducted to rule out a pituitary mass or other intracranial cause of central diabetes insipidus and was negative for any defect. Pertinent initial labs include BUN 8mg/dL, creatinine 1.18mg/dL, glucose 164mg/dL, sodium 147mEq/L, potassium 3.8mEq/L, and calcium 9.8mg/dL. After Precedex was started, pertinent labs included BUN 39mg/dL, creatinine 1.39mg/dL, glucose 201mg/dL, sodium 181mEq/L, potassium 4.3mEq/L, and calcium 9.1mg/dL. The serum vasopressin levels were measured at 1.1pg/mL (normal range 0.0-6.9pg/mL).

A review of the patient's hospital course showed that the administration of dexmedetomidine due to intolerance of previous sedation methods was the only addition, and that the onset of the polyuria was during the IV infusion. After the drug had been stopped, the urine output spontaneously decreased to previous levels and the urine osmolality increased to 541mOsm/kg H_2O. The serum osmolality also began to trend down over the next few days to 337mOsm/kg. The patient was not re-started on Precedex. Other reasons for hypernatremia were excluded.

We determined after reviewing the clinical course that the polyuria was due to central diabetes insipidus secondary to dexmedetomidine (Precedex) infusion. One way the probability of an adverse drug reaction can be determined is through the Naranjo scale [10]. The score for dexmedetomidine induced polyuria for this patient was a 7, a result of "probable likelihood" that the medication was indeed responsible for this adverse reaction.

Discussion

Polyuria is defined as a urine output of greater than 3 liters with a range of etiologies including primary polydipsia, decreased ADH secretion due to central diabetes insipidus, decreased peripheral ADH sensitivity due to nephrogenic diabetes insipidus (NDI), and solute diuresis such as glucosuria [11]. Usually, hypernatremia as evidenced by this patient points to central or nephrogenic diabetes insipidus as the cause, especially in the absence of diabetes mellitus and diuretics. Furthermore, an abrupt onset is particularly indicative of central diabetes insipidus as it takes time for the impaired renal tubule to become unable to concentrate urine in response to vasopressin in NDI. Briefly, under physiologic conditions, ADH increases water retention by the kidneys by increasing the permeability of the distal collecting duct to water via V2 receptors, and thus plays an important role in regulating homeostasis. Typically, when osmoreceptors in the hypothalamus sense an increased osmotic pressure, or when baroreceptors sense a decrease in fluid volume, ADH is

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secreted by the posterior lobe of the pituitary gland. Because ADH is synthesized within the hypothalamus, most cases of central diabetes insipidus involve the loss of neurosecretory neurons in the supraoptic and paraventricular nuclei.

Dexmedetomidine is a highly selective alpha2-agonist used to treat delirious patients in intensive care units around the nation, as well as for adjunctive therapy for sedation. This class of medication is particularly useful for anxiolysis, analgesia, and sedation without the side effects of respiratory depression or significant cognitive impairment [12]. Research has shown that this agent inhibits the release of norepinephrine by targeting the locus coeruleus in the pons, near the floor of the fourth ventricle [6]. This mechanism of action mimics that of locus coeruleus lesions, in which secretion of ADH is decreased [3,13]. As mentioned above, a decrease in ADH or vasopressin levels can lead to polyuria secondary to central diabetes insipidus. However, there have been some animal studies that have specifically examined the mechanisms of dexmedetomidine induced polyuria [14-17]. This included the possibility that the medication inhibits ADH release from the paraventricular nucleus and paraventricular magnocellular neurosecretory neurons of the hypothalamus. As already discussed, this is the cause of central diabetes insipidus. Another approach involves more peripheral activity in which dexmedetomidine acts on the renal tubules and releases renin or atrial natriuretic peptide, desensitizing the response of the kidney to ADH. There is also another hypothesis that dexmedetomidine also has activity on imidazoline receptors in other parts of the kidney, which increases sodium and water excretion without the involvement of ADH. This particular mechanism would lead to elevated serum sodium levels and serum osmolality. In our patient, ADH serum levels were on the low-end of normal after administration of dexmedetomidine, and because these levels were not continuously measured throughout the hospital course, no definite conclusion can be made about the mechanism of action for this particular case.

While there are many hypotheses for the role of dexmedetomidine in inducing polyuria secondary to transient central diabetes insipidus, there have not been many reported cases. A literature review was conducted and we identified 15 reported cases of possible dexmedetomidine induced polyuria (Table 1). While two texts were inaccessible, nine of the remaining 13 cases occurred in the setting of anesthesia during surgery. Interestingly, in four of those, patients underwent spinal fusion surgery [2,4,5,18]. Patients also experienced polyuria in the setting of other surgeries such as maxillofacial surgery and tumor resection. The relationship between certain types of surgeries and dexmedetomidine induced polyuria warrants further investigation. While there seems to be more representation, thus, in the anesthesia literature, intensive care unit cases are much more rare. Our case was one of only four others which occurred in the ICU [6,7,19].

Study	Infusion Rate	Onset of Diuresis	Setting	Other methods of sedation
Adams, et al. [25]	Text unavailable			
Charran, et al. [26]	0.2 mcg/kg/hr	Immediately after infusion started	ICU	-
Chen, et al. [3]	0.6 μg/kg bolus	30 min	Dissection of the tongue, mandible, and neck	Propofol, sufentanil, sevoflurane, and rocuronium
Chow, et al. [7]	-	Within 24 hours	ICU	Propofol
Granger, et al. [2]	1.0 μg/kg bolus and 1 continuous	60 min	Anterior cervical discectomy and fusion	Propofol, remifentanil, midazolam
Greening, et al. [18]	0.5 continuous	Within 60 min	Laminectomy and spinal fusion	Gabapentin, midazolam, lidocaine, isoflurane, vecuronium, sufentanil, propofol, ketamine
Haldar, et al. [21]	1 μg/kg bolus and 0.3-0.5 continuous	Beginning of surgery	Endoscopic excision of tuberculum sellae meningioma	Propofol, fentanyl, sevoflurane, atracurium
Ji, et al. [4]	0.4 continuous	60 min	Posterior spinal fusion and instrumentation	Propofol, fentanyl, midazolam, and rocuronium

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Kirschen, et al. [5]	0.5 continuous	30 min	Cervical fusion	Propofol, fentanyl, midazolam, ketamine, succinylcholine, lidocaine
Pratt, et al. [19]	2.0 continuous	120 min	ICU	Midazolam
Selvaraj, et al. [20]	0.25 μg/kg bolus and 0.3 continuous	30 min	Mandibulectomy	Propofol, morphine, vecuronium
Singh, et al. [24]	Text unavailable			
Takekawa, et al. [23]	0.4 μg/kg/hr	120 min	Superficial parotidectomy in the setting of schizophrenia	Roxatidine, diazepam, propofol, remifentanil, fentanyl, succinylcholine
Uddin, et al. [6]	0.2 mcg/kg/hr	Immediately after infusion had finished	ICU	None
Xu, et al. [22]	0.6 μg/kg bolus	60 min	Left thigh sarcoma resection	Etomidate, sufentanil, sevoflurane, remifentanil, cisatracurium, ropivacaine
Present Case	0.5 mcg/kg/hour	While receiving the medication	ICU	Propofol, fentanyl

Table 1: Literature review of dexmedetomidine induced polyuria cases.

One factor that was analyzed among the different cases was other methods of sedation used, as research has shown that propofol and sevoflurane can also cause polyuria [27-29]. However, in our case, propofol was used both before and after the administration of dexmedetomidine, and there was no evidence of polyuria during those times. In fact, as propofol was continued again, the diuresis amount decreased. Sevoflurane was not used on our patient. Therefore, it is safe to say that other methods of sedation did not lead to his polyuria. Only one other ICU case used either one of these and in that case, polyuria was also only observed after the patient was placed on dexmedetomidine for alcohol withdrawal [7].

When comparing the infusion rates and onset of polyuria, our case was the only one in which diuresis started while receiving the infusion. For the other cases in the ICU, only one other case had immediate onset polyuria, but this was right after the infusion had been completed [6]. Our patient was given a continuous infusion of 0.5mcg/kg/hour and diuresed 425cc within the first 30 minutes of infusion. While other cases in the literature had higher doses of infusion, onset of polyuria was a few hours later. Therefore, there seems to be no correlation between the infusion rate and loading dose. Kirschen et al. showed that there in fact was no dose-dependent relationship between the infusion rate and polyuria (R^2=0.308) [5].

Conclusion

As dexmedetomidine is used more frequently in intensive care units throughout the world, critical care physicians should become increasingly aware of this potentially severe side effect of the drug. Urine output, osmolality and serum electrolytes should be monitored closely while the patients in the intensive care unit receive Precedex. Furthermore, this adverse effect should be considered when determining the differential mechanisms for polyuria in the intensive care unit or in the operating room.

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