Secondary adrenal insufficiency induced by long-term use of opioid analgesics

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ABSTRACT

The effects of long-term use of opioid analgesics on the hypothalamic-pituitary-adrenal axis are not well recognized. We report a 41-year-old woman on chronic opioid therapy hospitalized for cardiovascular collapse following a right stellate ganglion nerve block. She developed severe hypotension after the procedure. Morning cortisol was low. The results from the cosyntropin test were consistent with secondary adrenal insufficiency. Her secondary adrenal insufficiency was likely due to long-term use of opioid analgesics for pain in the absence of other etiologies.

KEYWORDS Adrenal insufficiency; hypothalamic-pituitary-adrenal axis; opioids

The USA is facing an opioid epidemic. In 2017, health care providers wrote 58.5 narcotic prescriptions per 100 persons.¹ Opioids play a role in pain management, but they also carry a wide range of adverse effects. Opioid-induced endocrinopathies are underappreciated, particularly opioid-induced adrenal insufficiency (AI). Opioid receptors are present in the pituitary gland and hypothalamus, and opioids may impact hypothalamic-pituitary-adrenal axis (HPA) function. We report a case of secondary AI related to long-term opioid dependency.

CASE PRESENTATION

A 41-year-old woman had chronic pain from a right brachial plexus injury caused by a motor vehicle accident. She had used opioid analgesics since her right arm was amputated 15 years earlier. She had a history of childhood asthma but indicated that this was not active, and she was not on any medications. The patient denied any history of fatigue, dizziness, nausea, or vomiting. Home medications included hydrocodone-acetaminophen 7.5 mg to 325 mg one tablet every 6 hours, tramadol 50 mg one tablet every 4 hours, and pregabalin 200 mg one capsule every 8 hours. No history of autoimmune disease or traumatic brain injury was reported. She also denied any exposure to exogenous steroids, including inhalers and injections.

The patient had an elective right stellate ganglion block procedure because of worsening pain. Shortly after the procedure, she developed cardiovascular collapse and respiratory distress and was admitted to the hospital. She breathed with difficulty; her oxygen saturation fell to 82% on room air, and her respiratory rate increased to 24 breaths/min. Her blood pressure fell to 77/50 mm Hg, with a heart rate of 79 beats/min and a temperature of 97.3°F. She had expiratory rhonchi.

Results of a complete blood cell count, chemistry panel, and renal and liver function panel were normal, as were troponin, brain natriuretic peptide, and D-dimer levels. Chest x-ray, electrocardiogram, and echocardiogram were normal. Her oxygen saturation improved with bronchodilators, and her blood pressure improved after 2 L of normal saline. However, her blood pressure remained marginal, with the highest reading noted to be 90/60 mm Hg. Blood, sputum, and urine cultures were negative. There was no obvious source of infection or blood loss. Her morning cortisol level was 0.5 µg/dL (reference range, 6.2–19.4 µg/dL). Cortisol levels increased to 19.7 µg/dL 60 minutes after intravenous cosyntropin (250 µg). Her basal adrenocorticotropic hormone was 6 pg/mL (reference range, 6–50 pg/mL).

Magnetic resonance imaging of the head with contrast revealed a normal pituitary gland. There was a dramatic improvement in her blood pressure after intravenous

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Received February 4, 2019; Revised March 20, 2019; Accepted March 21, 2019.

hydrocortisone. She was discharged home on oral hydrocortisone 15 mg in the morning and 5 mg in the evening. At 1-month follow-up she reported improved well-being.

DISCUSSION

Patients with secondary AI usually present with symptoms such as nausea, dizziness, and fatigue. Hypotension and adrenal crisis may occur.² It is well established that cortisol can increase after cosyntropin stimulation in secondary hypoadrenalism. Some have used 20 ng/mL as the cutoff for serum cortisol. However, even a cortisol value above this should not preclude treatment with glucocorticoids if the clinical presentation is consistent with cortisol deficiency.³ Moreover, even low-dose cosyntropin testing may not predict response to glucocorticoids⁴ and thus initial cosyntropin testing may miss secondary cortisol deficiency.⁵ We agree with Burgos et al⁶ that the patient's clinical presentation should be considered when interpreting cosyntropin tests. We believe that glucocorticoid treatment should not be withheld on the basis of a cortisol level if the clinical presentation is consistent with hypoadrenalism.

Secondary AI has a broad differential and includes exogenous glucocorticoid therapy as the most common etiology. Our patient denied any exposure to exogenous steroids. We also could not find any other etiologies, including brain injury, as possible causes for the secondary AI and, as such, long-term opioid exposure was the most likely etiology.

Opioid-induced AI has been reported but is not well recognized. Dackis et al reported reduced adrenocorticotrophic hormone and cortisol levels in methadone-addicted individuals.⁷ Delitala et al studied the effect of naloxone infusion on the HPA axis and reported an increase in cortisol levels. Opioids may mediate an inhibitory effect on the HPA axis.⁸ Delitala et al also observed a fall in cortisol levels after morphine use.⁸ Nenke et al studied 17 patients treated with long-term (>4 weeks) opioids. Five of the 17 (29%) were found to have evidence of AI, with cortisol levels of <5 µg/dL.⁹ Additionally, Oltmanns et al observed improved HPA axis function after reduction of a transdermal fentanyl dose.¹⁰

Treatment options for AI include eliminating opioids, reducing the dosage, and starting corticosteroid replacement. We suggest that physicians prescribing long-term opioids educate patients about endocrine-related adverse effects such as hypoadrenalism and hypogonadism. Finally, the

interaction between opiates and the HPA axis appears complex; with the current opioid epidemic, we expect more emerging cases of opioid-induced AI.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of the Clinical Research Institute at Texas Tech University Health Science Center.

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