Opioid-Induced Secondary Adrenal Insufficiency in a Young Patient with Chronic Pancreatitis

Amry Majeed, Nicholas Noverati, MD, Christine Kurian, MD, Shirin Jaggi, DO

INTRODUCTION

Opioid misuse is a national public health crisis that has contributed to a decrease in life expectancy in men and women in the US. From 1999-2017, the rate of drug overdose deaths tripled, largely due to the rise in opioid use[1]. Despite widespread misuse, chronic opioid therapy still has a role in the clinical setting. Adverse effects include dizziness, nausea, vomiting, respiratory depression, and dependence[2]. While these side effects are well-documented, other effects of opioids are less explored, including opioid-induced adrenal insufficiency[3,7]. The typical presentation of adrenal insufficiency from any cause can include fatigue, nausea, vomiting, weight loss, abdominal pain and muscle aches. Laboratory findings might include hyponatremia and hyperkalemia. This case, however, presents a patient with atypical presentation but confirmed diagnosis of adrenal insufficiency in the setting of chronic opioid use. Ultimately, given chronic opioid use both prescribed and unprescribed, it is imperative that healthcare providers understand the endocrine effects of opioids as adrenal insufficiency is associated with higher morbidity and mortality[3].

The adrenal gland is made up of a cortex and medulla which each produce vital hormones. Specifically, the cortex is responsible for producing glucocorticoids, mineralocorticoids, and androgens. Destruction or dysfunction of the adrenal gland may lead to deficiency of these hormones. Adrenal insufficiency can be classified into primary, secondary, or tertiary types. Primary adrenal insufficiency denotes malfunctioning of the adrenal gland itself. Secondary adrenal insufficiency is characterized by a decreased level of adrenocorticotropin (ACTH) released by the pituitary gland. Tertiary adrenal insufficiency is defined by a decreased level of corticotropin-releasing hormone (CRH) from the hypothalamus[15]. Opioids bind to mu, kappa, and delta opioid receptors to create effects throughout the body, including on the hypothalamus and pituitary. This is the proposed mechanism for opioid-induced suppression of the hypothalamus-pituitary-adrenal (HPA) axis noted in some studies[3].

NARRATIVE

A 33 year-old man with a past medical history of chronic pancreatitis secondary to heavy alcohol use presented to the hospital with a chief complaint of abdominal pain, nausea, vomiting, and poor appetite. During the hospitalization, the patient was hydrated with intravenous fluids and pain control was optimized. Since his initial diagnosis of pancreatitis, his home analgesics included oxycodone 10 mg, gabapentin 800 mg and duloxetine 60 mg. On admission his oxycodone was discontinued and he was started on hydromorphone through a patient-controlled analgesia pump as well as a ketamine infusion titrated by an acute pain management team. During endoscopy to perform a celiac plexus nerve block, findings consistent with chronic calcific pancreatitis were noted. With this procedure, his pain was better controlled and he was transitioned back onto an oral opioid-containing pain control regimen with oxycodone 10 mg, gabapentin 900 mg, and duloxetine 60 mg. However, his hospital course was further complicated by uncontrolled hypertension and fluctuating blood sugars.

His blood glucose readings were initially as high as 500 mg/dL, at which point an insulin infusion was initiated for better control. The patient did not have evidence of diabetic ketoacidosis. The infusion was eventually discontinued and the patient was transitioned to a basal bolus insulin regimen.

The patient's blood pressure was also difficult to control. His home medications included carvedilol 3.125 mg, hydralazine 100 mg, nifedipine 60 mg, losartan 100 mg, and a clonidine patch 0.3 mg. Due to his inability to tolerate medications by mouth secondary to nausea, the patient was taking these medications inconsistently.

Although his poorly controlled blood sugars and pressures were thought to be in part due to his abdominal pain, a secondary workup was pursued, especially considering his extensive multi-drug regimen. This workup included an aldosterone:renin ratio, urine and serum metanephrines, and a morning cortisol level. Due to hypertension and hyperglycemia, as well as normal serum sodium (136 mmol/L) and potassium (4.0 mmol/L), suspicion for adrenal insufficiency was low. However, the morning cortisol level was low at 2.3 mcg/dL. A cosyntropin stimulation test confirmed adrenal insufficiency; cortisol levels only increased to 10.8 mcg/dL after 60 minutes. A baseline ACTH level was found to be low at <9 pg/mL. Other lab findings were significant for normal values of sodium (136 mmol/L) and potassium (4.0 mmol/L). Since this was a surprising finding given the lack of clinical signs and symptoms of adrenal insufficiency, the stimulation test was repeated with similar results. The patient was

started on prednisone 5 mg daily and instructed to follow up with Endocrinology within 2 months to repeat a cosyntropin stimulation test to reassess his hypothalamic-pituitary-adrenal (HPA) axis. The leading differential of this atypical presentation of secondary adrenal insufficiency was thought to be due to his history of chronic opioid use.

DISCUSSION

Opioids have widespread effects on the body, but their impact on the HPA axis is not well understood. There have been a few studies and case reports that have demonstrated opioid-induced adrenal insufficiency. One review concluded that 9% to 29% of patients receiving long-term opioids develop adrenal insufficiency[3,7]. Two clinical trials showed that treatment with naloxone, an opioid antagonist, led to increased cortisol levels and an augmented response to corticotropin-releasing hormone (CRH)[4,5]. These findings suggest that opioids suppress the hypothalamic-pituitary-adrenal axis[3]. Animal studies have shown mixed findings in regards to the effect of opioids on the HPA axis. In two animal studies, a single injection of morphine led to higher levels of corticotropins and glucocorticoids[10,11]. In contrast, long-term administration of opioids had variable effects on the HPA axis in rats. One study showed low doses of intraperitoneal morphine demonstrated adrenal insufficiency in rodents, whereas rats treated with increasing doses of intravenous morphine (10-100 mg/kg) twice a day for 16 days were found to have elevated corticosterone levels[12]. While most human studies have shown suppression of the HPA axis in the setting of chronic opioid use, one study analyzing 39 patients with chronic opioid use showed hyperfunctioning of the HPA axis[13]. Individual differences in the impact of chronic opioid use on the HPA axis may be attributed to variation in opioid receptor polymorphism that may alter affinity[14].

This is a unique case of opioid-induced adrenal insufficiency because the patient lacked the classic lab findings associated with adrenal insufficiency including hypotension, hyponatremia, hyperkalemia, and/or hypoglycemia. In fact, he was persistently hypertensive and hyperglycemic. The most common etiology of secondary adrenal insufficiency is exogenous glucocorticoids[8]. Our patient had no history of glucocorticoid use. Treatment of opioid-induced adrenal insufficiency includes glucocorticoid administration[3]. Case reports have shown that discontinuation of opioids may reverse the adrenal insufficiency[3,9,13]. Because there are currently no screening guidelines for adrenal insufficiency in patients with chronic opioid use, this endocrinopathy is likely underreported. This case highlights the notion that the clinical presentation of adrenal insufficiency may not always manifest with the classic signs of hypoadrenalism. However, it is critical that this effect of opioids is considered given that the clinical manifestations of adrenal insufficiency may be masked by concurrent illness[6].

CONCLUSION

Chronic opioid use is common, and may be underreported by patients due to non-prescription use. In addition to many well-known risks of chronic opioid use, opioids can affect the HPA axis. Healthcare providers and patients should be alert for the possibility of adrenal insufficiency with long-term use of opioids. Adrenal function should be monitored in these patients, and glucocorticoids should be administered whenever necessary.

REFERENCES

1. Singh G, Kim, Jr. I, Girmay M et al. Opioid Epidemic in the United States: Empirical Trends, and A Literature Review of Social Determinants and Epidemiological, Pain Management, and Treatment Patterns. *International Journal of MCH and AIDS (IJMA)*. 2019;8(2):89-100. doi:10.21106/ijma.284
2. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2 Suppl):S105-S120.
3. Donegan D, Bancos I. Opioid-Induced Adrenal Insufficiency. *Mayo Clin Proc*. 2018;93(7):937-944. doi:10.1016/j.mayocp.2018.04.010
4. Delitala G, Devilla L, Arata L. Opiate receptors and anterior pituitary hormone secretion in man. Effect of naloxone infusion. *Acta Endocrinol (Copenh)*. 1981;97(2):150-156. doi:10.1530/acta.0.0970150
5. Allolio B, Schulte HM, Deuss U, Kallabis D, Hamel E, Winkelman W. Effect of oral morphine and naloxone on pituitary-adrenal response in man induced by human corticotropin-releasing hormone. *Acta Endocrinol (Copenh)*. 1987;114(4):509-514. doi:10.1530/acta.0.1140509
6. Lee AS, Twigg SM. Opioid-induced secondary adrenal insufficiency presenting as hypercalcaemia. *Endocrinol Diabetes Metab Case Rep*. 2015;2015:150035. doi:10.1530/EDM-15-0035
7. Li T, Cunningham JL, Gilliam WP, Loukianova L, Donegan DM, Bancos I. Prevalence of Opioid-Induced Adrenal Insufficiency in Patients Taking Chronic Opioids. *J Clin Endocrinol Metab*. 2020;105(10):dgaa499. doi:10.1210/clinem/dgaa499
8. Ali ES, Peiris AN. Secondary adrenal insufficiency induced by long-term use of opioid analgesics. *Proc (Bayl Univ Med Cent)*. 2019;32(3):417-418. Published 2019 May 21. doi:10.1080/08998280.2019.1600180
9. Tabet EJ, Clarke AJ, Twigg SM. Opioid-induced hypoadrenalism resulting in fasting hypoglycaemia. *BMJ Case Rep*. 2019;12(12):e230551. Published 2019 Dec 11. doi:10.1136/bcr-2019-230551
10. Jezová D, Vigas M, Jurcovicová J. ACTH and corticosterone response to naloxone and morphine in normal, hypophysectomized and dexamethasone-treated rats. *Life Sci*. 1982;31(4):307-314. doi:10.1016/0024-3205(82)90407-6
11. Buckingham JC, Cooper TA. Differences in hypothalamo-pituitary-adreno-cortical activity in the rat after acute and prolonged treatment with morphine. *Neuroendocrinology*. 1984;38(5):411-417. doi:10.1159/000123927
12. Houshyar H, Cooper ZD, Woods JH. Paradoxical effects of chronic morphine treatment on the temperature and pituitary-adrenal responses to acute restraint stress: a chronic stress paradigm. *J Neuroendocrinol*. 2001;13(10):862-874. doi:10.1046/j.1365-2826.2001.00713
13. Rhodin A, Stridsberg M, Gordh T. Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clin J Pain*. 2010;26(5):374-380. doi:10.1097/AJP.0b013e3181d1059d
14. Wand GS, McCaul M, Yang X, et al. The mu-opioid receptor gene polymorphism (A118G) alters HPA axis activation induced by opioid receptor blockade. *Neuropsychopharmacology*. 2002;26(1):106-114. doi:10.1016/S0893-133X(01)00294-9
15. Huecker MR, Dominique E. Adrenal Insufficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing; December 1, 2020.