Lessons from practice

Severe hypoglycaemia secondary to chronic opioid-induced hypothalamic–pituitary–adrenal axis suppression: an under-recognised phenomenon

Clinical record

A 49-year-old woman with type 2 diabetes mellitus was hospitalised with critical hypoglycaemia (blood glucose level, 0.9 mmol/L; reference interval [RI], 3.5–5.4 mmol/L). The hypoglycaemia was initially attributed to reduced oral intake and her insulin regimen (NovoMix 30, 40 units twice daily). However, persistent hypoglycaemic episodes, despite insulin discontinuation, required intravenous dextrose boluses over a 12-hour period. Comorbidities included obesity (body mass index, 30.4 kg/m^2), hypertension and migraines managed with codeine and oxycodone at a dose equivalent to 80 mg of oral morphine per day. This raised suspicion of opioid-induced central adrenal insufficiency (OIAI). She denied weight loss and nausea; however, reported significant lethargy.

The diagnosis of OIAI was supported by a critically low morning serum cortisol level (9 nmol/L; RI, 155–599 nmol/L), and an adrenocorticotropic hormone (ACTH) level less than 1 ng/L (RI, 7.2–63.3 ng/L). Thyroid function was normal (thyroid-stimulating hormone, 3.5 mIU/L; RI, 0.27–4.2 mIU/L; free thyroxine, 13.1 pmol/L; RI, 12.0–22.0 pmol/L) with suppressed gonadotrophins. The patient was taking the combined oral contraceptive pill (OCP). A magnetic resonance imaging scan of the pituitary showed normal anatomy, with no sellar mass or radiological signs of hypophysitis.

The patient was commenced on hydrocortisone (20 mg morning, 4 mg midday, 4 mg evening) and was counselled on sick day management. Insulin doses (NovoMix 30) were reduced to 32 units twice daily and the OCP was no longer given. Neurologist-led efforts to reduce the patient's opioid intake were unsuccessful due to poor response to alternative migraine treatments. Her lethargy improved and no further hypoglycaemic episodes occurred. Low ACTH levels with peak cortisol levels of 200 nmol/L (RI, > 450 nmol/L) on cosyntropin stimulation tests (CSTs) conducted at the one-year and six-year marks confirmed unresolved chronic OIAI, warranting indefinite hydrocortisone therapy.

Discussion

Hypoglycaemia in type 2 diabetes mellitus is typically attributed to antidiabetic medications; however, the diagnosis of adrenal insufficiency, although rare, should be considered in severe or prolonged hypoglycaemia.[1] The clinical manifestations of adrenal insufficiency can be non-specific and resemble those caused by opioid therapy and the underlying conditions requiring opioid treatment. Other causes of adrenal insufficiency such as space-occupying lesions, pituitary apoplexy, head trauma and drug-induced adrenal insufficiency, including exogenous steroids, were absent in the patient and should be excluded.[2] Notably, the patient's serum cortisol level was strikingly low despite OCP use, which elevates total cortisol concentrations by increasing corticosteroid-binding globulin.[3]

Chronic opioid use is widespread in Australia, with 3.1 million Australians prescribed opioids in 2016–17, predominantly oxycodone.[4] However, prevalence data of OIAI stem from small, retrospective studies with significant variability in clinical contexts, opioid dosages, therapy duration and administration routes.[5] Consequently, chronic opioid use remains an under-recognised cause of adrenal insufficiency.

Opioid-induced hypothalamic–pituitary–adrenal (HPA) axis suppression is thought to occur through the inhibition of corticotropin-releasing hormone (CRH) via central G protein-coupled opioid receptors.[6] Additionally, opioids act on pancreatic opioid receptors, activate the sympathetic nervous system, and modulate glucoregulatory hormones including insulin, glucagon, epinephrine and cortisol.[7] Individual susceptibility may vary due to differences in opioid receptor affinity or interleukin-1β function on CRH.[6]

Consistent with our report, OIAI appears to be dose-dependent with affected patients typically using daily morphine-equivalent doses exceeding 60 mg.[8]

Patients suspected of having OIAI should have the following tests: an 8 am to 9 am serum cortisol level test, an ACTH level test, and a 250 μg CST. A low baseline ACTH level indicates a central aetiology. International guidelines provide estimated thresholds for diagnosing adrenal insufficiency, including a morning cortisol level of less than 83 nmol/L and a peak cortisol level of less than 500 nmol/L in response to the CST. However, significant interassay variability underscores the importance of adhering to local laboratory-specific thresholds.[9] These thresholds have only been retrospectively assessed in OIAI cases. Until further research is available, we recommend applying these thresholds to OIAI.[10]

There is limited literature guiding the management of OIAI. Hydrocortisone should be commenced at a dosage of 15–20 mg daily, divided into 2 to 3 doses, with the largest dose taken on waking.[9]

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Although data on HPA axis recovery in OIAI are scarce, small case series indicate that up to 70% of patients may experience rapid recovery following opioid withdrawal.[11] Chronic opioid use should be tapered gradually, with hydrocortisone therapy continued until HPA axis recovery is confirmed. However, the minimum opioid dose needed for HPA axis recovery and the timeline for this process remain uncertain, highlighting the need for alternative analgesic agents.[12,13]

This near-fatal case underscores the importance of recognising opioid-induced HPA axis suppression in the current era of widespread opioid use while maintaining awareness of the endocrine effects of opioids. There remains a significant gap in data regarding the impact of opioids on the hypothalamus and pituitary, highlighting the need for further research to improve the prevention and treatment of HPA axis suppression in people with chronic opioid use and complex comorbidities such as diabetes mellitus.

Lessons from practice

- Consider opioid-induced adrenal insufficiency (OIAI) as a potential cause of severe hypoglycaemia in patients on chronic opioid therapy.
- Standard guidelines for diagnosing adrenal insufficiency, including morning cortisol measurements and adrenocorticotropic hormone stimulation tests, may be applied but have not been prospectively validated in opioid-treated patients.
- Hydrocortisone is recommended for the management of OIAI, and tapering opioid use is advised when aiming for the restoration of hypothalamic–pituitary–adrenal (HPA) axis function.
- A significant knowledge gap exists regarding the mechanisms underlying opioid-induced HPA axis suppression and the timeline for its recovery.

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