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Insulinoma mimic: methadone-induced hypoglycaemia

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SUMMARY

Methadone use for opioid use disorder and chronic pain has increased since the start of the century with about 4.4 million dispensed prescriptions in 2009. With increased use of methadone, there has been increasing reporting of less commonly reported side effects (ie, hypoglycaemia). Here, we describe a woman in her 70s with history of opioid use disorder on methadone, stage 4 chronic kidney disease and prior hypoglycaemic episodes who initially presented with perforated gastric ulcer requiring surgical repair. Her perioperative course was complicated by profound hyperinsulinaemic hypoglycaemia. Given concern for methadone-induced hypoglycaemia, methadone was discontinued with monitoring of subsequent blood glucose, insulin, C peptide, proinsulin, β -hydroxybutyrate and blood methadone levels. As the serum methadone levels decreased, insulin levels substantially decreased in parallel. After 21 days off methadone, dextrose infusion was discontinued with restoration of euglycaemia. In a patient with hyperinsulinaemic hypoglycaemia and methadone use, it is important to consider discontinuing methadone and re-evaluate fasting glucose levels prior to an extensive and invasive insulinoma workup.

BACKGROUND

Methadone, a pharmacological agent for treatment of opioid use disorder and chronic pain, has been prescribed since the 1960s with increased use over the past 10 years.^{1,2} According to the Centers for Disease Control and Prevention, about 4.4 million prescriptions of methadone were dispensed in 2009.¹ Common adverse effects of methadone include constipation, nausea, bradycardia, QTc prolongation and respiratory depression.

Interestingly, there have been observations of hypoglycaemia in the setting of high dose methadone use. Methadone is a μ -opioid receptor agonist that acts centrally and peripherally. It also modulates nociceptive input through its effect on serotonin, norepinephrine and *N*-methyl-D-aspartate receptors.^{3,4} Possible aetiologies of hypoglycaemia may include promotion of pancreatic insulin release,⁵⁻⁸ suppression of counter-regulatory mechanisms such as glucagon, epinephrine and sympathoadrenal responses to hypoglycaemia^{9,10} as well as impairment of glycogenolysis and gluconeogenesis.^{11,12}

In mouse models, methadone significantly lowered blood glucose in a dose-dependent manner at doses greater than 10 mg/kg.¹³ Clinical observations of methadone-induced hypoglycaemia have been documented in retrospective studies and case reports^{12,14-23} and occurred in situations

of overdose when methadone doses were escalated.^{19,20,24} A retrospective study of the Food and Drug Administration Adverse Event Reporting System from 2004 to 2012 showed significantly increased odds of hypoglycaemia in tramadol and methadone compared with the use of other opioids, such as codeine, hydrocodone, oxycodone, hydro-morphone, morphine and fentanyl.^{12,25}

The objective of our study is to report a case of recurrent hypoglycaemia associated with endogenous hyperinsulinaemia in the setting of high dose methadone, which, to our knowledge, is the first report of its kind. This case uniquely demonstrates normalisation of blood glucose levels through repeated supervised fasts after methadone was held, a finding not reported in current literature.

CASE PRESENTATION

A woman in her 70s was admitted following acute onset of abdominal pain from perforated gastric ulcer. The perioperative period was notable for profound hypoglycaemia. She has a history significant for opioid use disorder and had been prescribed methadone for over three decades, incidentally found hepatitis C infection with spontaneous clearance without cirrhosis, class 2 obesity with a body mass index (BMI) of 38 kg/m², hypertension and stable stage 4 chronic kidney disease (CKD) of unclear aetiology. She reported episodes of confusion, non-sensical speech, blurry vision and diaphoresis that occurred when skipping a meal. Those symptoms did not occur when she ate three meals per day with a snack at bedtime. She had two prior evaluations for hypoglycaemia 4 and 2 years before her current admission at outside hospitals.

INVESTIGATIONS

Four years prior to her current admission, she presented with transient right arm weakness with a point-of-care (POC) glucose of 20 mg/dL. She had resolution of her symptoms with intravenous dextrose. A CT scan of the head without contrast did not show acute changes. With a serum glucose of 3.2 mmol/L (58 mg/dL), an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m² and a serum creatinine of 229.9 μ mol/L (2.6 mg/dL, similar to her baseline value), she had an insulin level of 18.5 μ U/mL and a C peptide of 1.89 ng/mL. The patient's glucose level rose by less than 1.4 mmol/L (25 mg/dL) following intravenous glucagon administration. Her home medications were methadone 115 mg daily and amlodipine 5 mg daily. She denied alcohol intake or illicit drug use.



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Sulfonylurea ingestion was ruled out with a negative hypoglycemic agent screen and insulin autoimmune syndrome was ruled out with a negative insulin autoantibody test. Non-invasive imaging techniques for insulinoma localisation, including CT and MRI studies of the abdomen with contrast, were contraindicated due to renal impairment. Endoscopic ultrasonography did not detect any pancreatic lesions. Based on these results, it was suspected that hypoglycaemia was multifactorial from methadone-induced hyperinsulinaemia and impaired clearance of methadone metabolites and gluconeogenesis from kidney dysfunction. Methadone was tapered down from 115 to 15 mg daily, which led to the resolution of hypoglycaemia.

Two years prior to her current admission, the patient was admitted to an outside hospital with confusion, blurry vision and diaphoresis. She had profound hypoglycaemia with a plasma glucose level of 1.8 mmol/L (33 mg/dL). She demonstrated pathological endogenous hyperinsulinaemia with an insulin level of 46.5 µU/mL and C peptide of 34.3 ng/mL. Her random cortisol level at 12:50 pm was 0.8 µmol/L (27 µg/dL), excluding adrenal insufficiency. During this admission her serum creatinine was 194.5 µmol/L (2.2 mg/dL) with an eGFR of 22 mL/min/1.73 m² when the insulinoma workup was initially sent. At that time, she was prescribed methadone 105 mg daily. The patient was started on prednisone 20 mg two times per day and methadone was tapered to 40 mg daily on discharge. By the end of her hospital stay, her glucose levels stably ranged from 4.4 mmol/L (80 mg/dL) to 7.7 mmol/L (140 mg/dL). She was advised to taper methadone and prednisone, and transition to buprenorphine/naloxone. The patient had received outpatient care outside our institution prior to her current admission; however, records were not accessible through our electronic medical record. Although the medical history provided by the patient was limited, she reports not completing evaluation besides the inpatient evaluations from prior to her current admission. She continued to have repeated episodes of confusion, non-sensical speech, blurry vision and diaphoresis that occurred when skipping a meal that she self-managed with frequent snacking while on methadone.

She presented with a perforated gastric ulcer which led to emergent surgery where she underwent a graham patch repair during her current admission. Her preoperative period was notable for symptomatic hypoglycaemia, with a nadir serum glucose level of 1.94 mmol/L (35 mg/dL). At this time, she was prescribed methadone 60 mg daily. Her weight on admission was 115 kg. Table 1 shows the patient's admission laboratory data.

The results of her complete blood count, CMP, cortisol (0.61 µmol/L or 22.2 µg/dL at 7:30 am), thyroid stimulating hormone (1.21 µIU/mL) and liver function tests were within normal limits. Her eGFR was 20–22 mL/min/1.73 m² at baseline, with a serum creatinine of 203.4 µmol/L (2.3 mg/dL). Serum and urine toxicology screening tests were negative except for methadone. Despite recovering after surgery and maintaining her caloric intake, the patient continued to be hypoglycaemic (blood glucose as low as 1.2 mmol/L or 36 mg/dL) 2 weeks later. At that time, she was switched to buprenorphine/naloxone.

Table 2 and figure 1 summarise the laboratory results during repeated supervised fasts for evaluation of hypoglycaemia in addition to diagnostic criteria for different causes of hypoglycaemia. Figure 2 illustrates the length of time the patient took to reach hypoglycaemia and corresponding serum methadone levels. Three days after methadone discontinuation, she was maintained on a solution of 50% dextrose in water infused at a rate of 25 mL/hour in addition to meals to maintain a target glucose level of 3.3 mmol/L (60 mg/dL).

Table 1 Laboratory values on admission of case study patient

Value	Reference range	Admission labs
Sodium (mmol/L)	135–148	145
Potassium (mmol/L)	3.5–5.1	4.6
Chloride (mmol/L)	96–109	108
Carbon dioxide (mmol/L)	21–31	23
Anion gap	7–16	14
Calcium (mg/dL)	8.4–10.5	8.0 (L)
Blood urea nitrogen (mg/dL)	7–22	21
Creatinine (µmol/L)	44.2–106.1	185.7 (H)
Estimated glomerular filtration rate (mL/min/1.73 m ²)	>60	25
Albumin (g/dL)	3.5–5.3	3.4 (L)
Alanine aminotransferase (U/L)	0–31	7
Aspartate aminotransferase (U/L)	0–31	17
Alkaline phosphatase (U/L)	30–120	99
Bilirubin, total (mg/dL)	0–1.2	0.4
White blood cells (K/mm ³)	4.5–11.0	16.8 (H)
Platelets (K/mm ³)	150–350	442 (H)
Haemoglobin (g/dL)	12–15	10.9 (L)
Thyroid stimulating hormone (µIU/mL)	0.5–4.5	1.2
Morning serum cortisol (µmol/L)	>0.4	0.6

Values include comprehensive metabolic panel and complete blood count as well as a morning serum cortisol level. Reference ranges are included.

The first monitored fast was conducted and found that after an hour after stopping the dextrose solution, her plasma glucose dropped to 2.9 mmol/L (52 mg/dL) with associated confusion and drowsiness. Additional labs drawn at the same time showed an insulin level of 7.4 µU/mL, C peptide of 1.05 ng/mL, proinsulin of 8.9 pmol/L and β-hydroxybutyrate (BHB) of 0.03 mmol/L. Serum methadone level was 610 ng/mL (therapeutic range 100–400 ng/mL). A serum creatinine was 247.6 µmol/L (2.8 mg/dL) and her eGFR was 19 mL/min/1.73 m². Serial serum methadone levels were obtained to evaluate the association between methadone levels and severity and aetiology of hypoglycaemia.

Five days after methadone discontinuation, the patient was maintained on a solution of 50% dextrose in water infused at a rate of 10 mL/hour to maintain glucose above 3.3 mmol/L (60 mg/dL). Seven hours after discontinuing the dextrose solution and her diet, her serum glucose dropped to 1.2 mmol/L (36 mg/dL), with an insulin level of 7.7 µU/mL, C peptide of 0.94 ng/mL, proinsulin of 7.9 pmol/L and BHB of 0.03 mmol/L. At this time, the patient's serum methadone level was 410 ng/mL. Her serum creatinine was 229.9 µmol/L (2.6 mg/dL) with an associated eGFR of 21 mL/min/1.73 m². The results of all three supervised fasts are shown in figures 1 and 2.

Fourteen days after methadone discontinuation, the patient's maintenance fluid was decreased to 20% dextrose in water infused at a rate of 30 mL/hour. Fourteen hours after stopping this solution and beginning the fast, her serum glucose dropped to 2.7 mmol/L (49 mg/dL), with an associated insulin level of 4.4 µU/mL, C peptide of 0.58 ng/mL, proinsulin of 4.7 pmol/L and BHB of 0.15 mmol/L. Her serum creatinine level was 247.6 µmol/L (2.8 mg/dL) and eGFR was 20 mL/min/1.73 m². Serum methadone level was 99 ng/mL.

She underwent endoscopic ultrasonography which did not detect distinct pancreatic lesions. A selective arterial calcium-stimulation test was attempted as an additional test for tumour

Table 2 Laboratory findings and clinical parameters from reported hypoglycaemia evaluations and in the case study patient

Expected results of a 72-hour fast					
Feature	Normal fast	Exogenous insulin administration	Oral hypoglycaemic agent administration	Insulinoma (glucose threshold <3.3 mmol/L)	Sensitivity/ specificity in insulinoma diagnoses
Symptoms*	Absent	Present	Present	Present	N/A
Glucose level (mmol/L)	-	--	--	<3.3	N/A
Insulin level (μ U/mL)	-	+++	+	>3	93%/95%
C peptide level (ng/mL)	-	-	+	≥ 0.6	100%/60%
β -Hydroxybutyrate level (mmol/L)	+++	-	-	≤ 2.7	100%/100%
Blood glucose response to glucagon	<1.4 mmol/L	≥ 1.4 mmol/L	≥ 1.4 mmol/L	≥ 1.4 mmol/L	91%/95%
Results of 72-hour fasts in the case study patient					
Feature	4 years earlier	2 years earlier	Day 0	Day +1	Day +10
Symptoms*	Absent	Present	Present	Present	Absent
Creatinine (μ mol/L); eGFR (mL/min/1.73 m ²)	2.6; N/A	2.2; N/A	2.8; 19	2.6; 21	2.8; 20
Glucose level (mmol/L)	3.2†	1.8	2.8	2.0†	2.7
Insulin level (μ U/mL)	18.5	46.5	7.4	7.7	4.4
Proinsulin level (pmol/L)	N/A	N/A	8.9	7.9	4.7
C peptide level (ng/mL)	1.89	34.3‡	1.05	0.94	0.58
β -Hydroxybutyrate level (mmol/L)	N/A	N/A	0.03	0.03	0.15
Blood glucose response to glucagon	<1.4 mmol/L	N/A	N/A	N/A	N/A
Serum methadone level (ng/mL)	N/A	N/A	610	410	99

*Symptoms include weakness and fatigue, resolving with dextrose administration.

†Serum lab value.

‡Laboratory error.

eGFR, estimated glomerular filtration rate; N/A, not applicable.

localisation. Insulin levels did not rise by twofold within 90 and 120 s of calcium stimulation in the distal splenic artery and proper hepatic artery, which would localise to the body and tail of pancreas; of note, however, most samples drawn were haemolysed and were unable to be used to detect insulin levels.

Twenty-one days after methadone discontinuation, the dextrose infusion was stopped without recurrence of hypoglycaemia. Serum methadone level was undetectable then. She was made NPO the following day for 24 hours and POC glucose checks showed stable readings ranging between 4.6 mmol/L (82 mg/dL) and 5.2 mmol/L (93 mg/dL). The

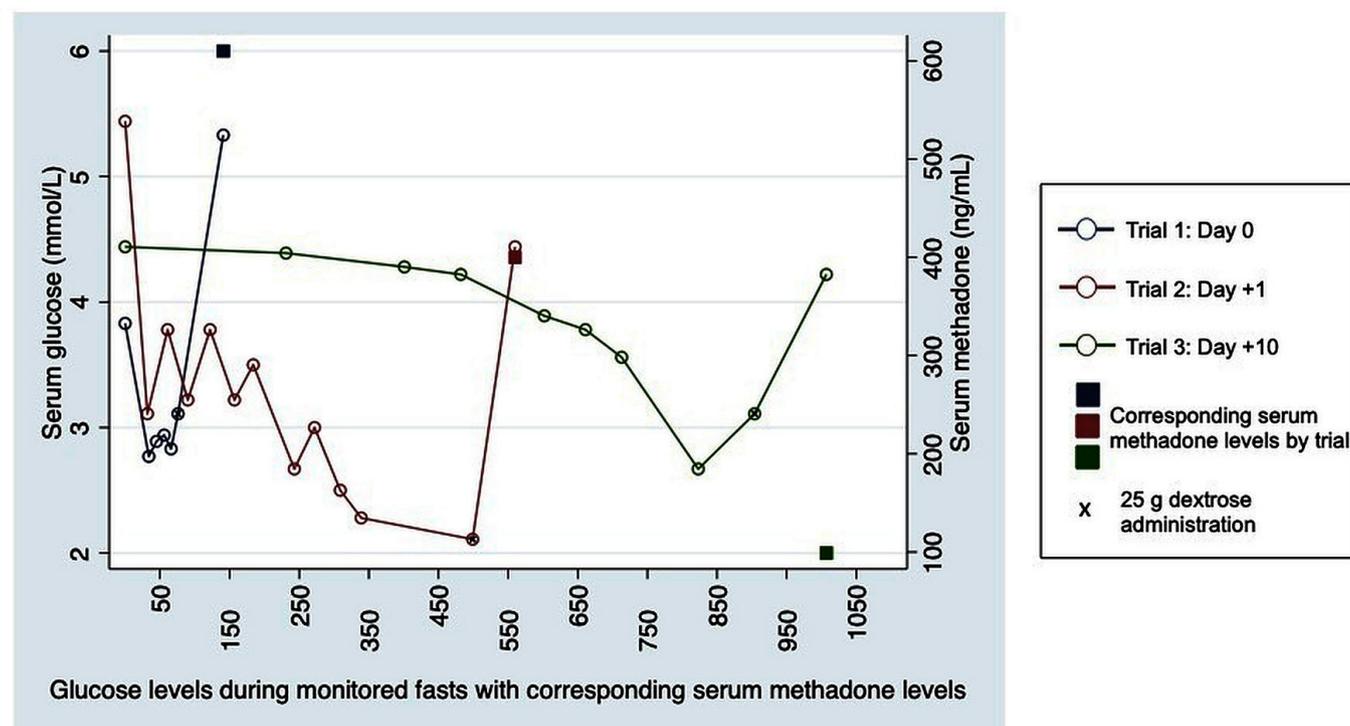


Figure 1 Glucose and methadone levels during three monitored fasts. The first trial is labelled day 0, the second trial occurred 1 day later (day +1) and the third trial took place 10 days later (day +10). Dextrose administration is indicated by the x and the blood glucose level following dextrose is included. Illustrated by Aanika Balaji.

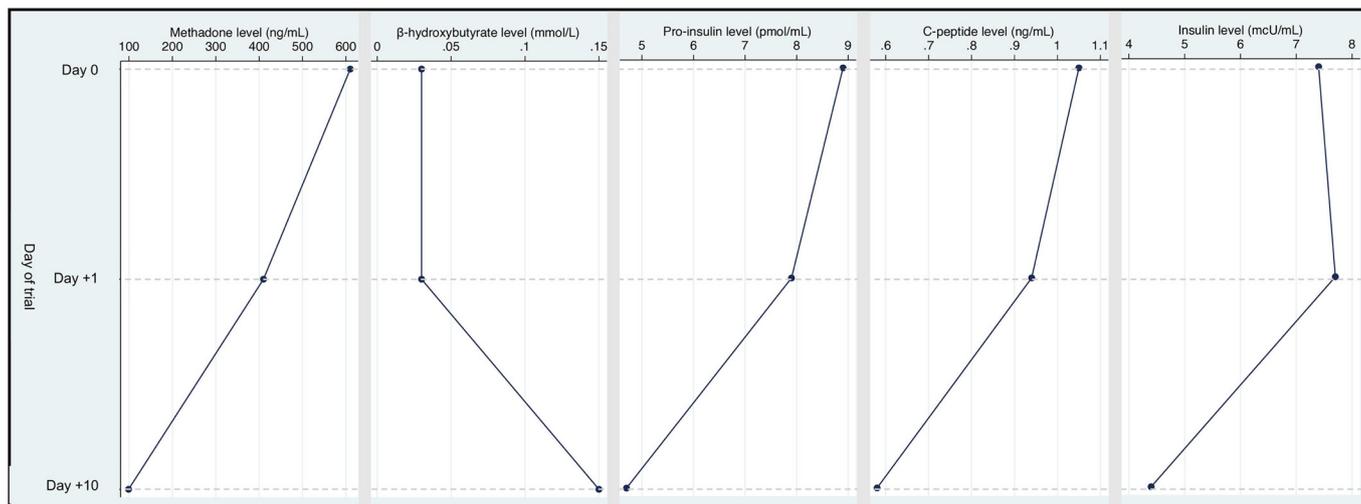


Figure 2 Insulinoma laboratory investigation among three monitored fasts. The first trial is labelled day 0, the second trial occurred 1 day later (day +1) and the third trial took place 10 days later (day +10). The laboratory values for insulin, C peptide, proinsulin, β-hydroxybutyrate and serum methadone levels are included for all three trials. Illustrated by Aanika Balaji.

patient was medically stable and was ultimately discharged. Her methadone prescription was changed to buprenorphine/naloxone.

OUTCOME AND FOLLOW-UP

The patient responded well to buprenorphine/naloxone without any side effects. About 6 months following her admission and the initiation of buprenorphine/naloxone, she reported that she no longer had abnormally low POC glucose levels or confusion when skipping a meal. Furthermore, her fasting POC glucose levels were in the 4.4–5.0 mmol/L (80–90 mg/dL) range.

DISCUSSION

This case demonstrated evidence of endogenous hyperinsulinaemia in a patient who had no localising pancreatic lesions with reversible hypoglycaemia as serum methadone levels tapered off, suggesting methadone-induced hyperinsulinaemic hypoglycaemia. Whipple's triad, a clinical trio of symptoms which suggests the presence of an insulinoma, was established by the presence of neuroglycopenic symptoms when her glucose was less than 3.1 mmol/L (55 mg/dL), with resolution of symptoms after treatment. When the plasma glucose concentrations were 1.8 mmol/L (33 mg/dL), 2.0 mmol/L (36 mg/dL) and 2.9 mmol/L (52 mg/dL), the insulin concentrations were greater than 3.0 μIU/mL and the C peptide concentrations were greater than 0.6 ng/mL, confirming endogenous hyperinsulinaemia. Although the patient has stage 4 CKD with an eGFR of 20–25, significant decreased renal insulin metabolism is not expected in a non-diabetic patient with renal disease until the eGFR level falls to less than 15–20 mL/min/1.73 m².^{26 27} Additionally, her serum creatinine levels and calculated eGFR drawn concurrently with insulinoma workups did not vary significantly and were near her baseline creatinine of 229.9 μmol/L (2.6 mg/dL), eGFR of 20–22 mL/min/1.73 m² (range: 194.5–247.6 μmol/L; eGFR 19–21 mL/min/1.73 m²). Therefore, renal insufficiency alone is unlikely to explain this degree of hyperinsulinaemic hypoglycaemia in this case.

The patient underwent repeat evaluations during multiple admissions, which excluded other causes of hypoglycaemia,

including exogenous insulin use, sulfonylurea ingestion and insulin autoimmune syndrome. There were several clinical findings that were not consistent with insulinoma. First, while on methadone, this patient did not respond to intravenous glucagon as plasma glucose concentration did not rise by at least 1.4 mmol/L (25 mg/dL) despite being well nourished (BMI 38 kg/m²) and having no evidence of hepatic synthetic dysfunction. Second, no discrete lesion was identified on endoscopic ultrasound. Third, during her final supervised fast when the methadone level decreased to 99 ng/mL, her C peptide and proinsulin levels were no longer inappropriately elevated, and glucose levels remained in normal range.

There are two retrospective studies^{20 23} and eight case reports of hypoglycaemia in the setting of methadone use.^{14–19 21 22} The lowest reported glucose level was 0.6 mmol/L (10 mg/dL),²² with a median of 2.2 mmol/L (40 mg/dL) and range between 0.6 mmol/L (10 mg/dL) and 2.4 mmol/L (44 mg/dL). Hypoglycaemia occurred during fasting states^{14–17} and were precipitated by methadone overdose,^{14 21 22} dose escalation^{17–20} and/or renal failure.^{15 17} The hypoglycaemia resolved with dose splitting,¹⁵ dose reduction^{17 19} or methadone discontinuation.^{14 17 18 21 22} When measured, insulin and C peptide levels were elevated.^{14 17}

Multiple case reports demonstrate a link between methadone use and hypoglycaemia. These case reports demonstrate hyperinsulinaemic hypoglycaemia occurring in patients aged 11 months to 51 years following ingestion of high doses of methadone.^{14 21 22} In the case described by Toce *et al*, a previously healthy 11-month-old boy who developed respiratory failure and hyperinsulinaemic hypoglycaemia after an acute, unintentional methadone exposure.¹⁴ With a blood glucose of 0.9 mmol/L (17 mg/dL) and serum methadone level of 123 ng/mL, insulin level was inappropriately elevated to 14.4 μIU/mL and serum BHB was suppressed to 0.22 mmol/L. Similar to our case presentation, testing for sulfonylurea and metabolic causes of hypoglycaemia was negative. An 18-hour fasting challenge was performed and the patient remained euglycaemic on hospital day 14 after methadone had been cleared from the child's system. We noted a similar phenomenon when our patient had low serum methadone levels, she remained euglycaemic for longer periods of time without

the need for dextrose supplementation. Li and colleagues reported the case of a woman in her 50s with opioid use disorder who presented with respiratory failure and refractory hypoglycaemia (2.1–2.6 mmol/L) 4 hours after the ingestion of 1000 mg of methadone.²¹ Dextrose was able to be weaned off 54-hours after ingestion. Fung *et al* presented a similar case of an otherwise healthy woman in her 20s who presented with altered mental status following the ingestion of 800 mg of methadone and was found to have hypoglycaemia with a blood glucose of 0.6 mmol/L (10 mg/dL).²²

Masharani *et al* outline the case of a woman in her late 30s with obesity, stage 3 CKD (eGFR 30–60) and back pain on methadone 160 mg every 6 hours as needed who presented with Whipple's triad.¹⁷ She had endogenous hyperinsulinaemia (insulin of 8.5 µU/mL, C peptide of 2.7 ng/mL, proinsulin of 49 pmol/L and BHB of 0.15 mmol/L) with a serum glucose level of 2.4 mmol/L (44 mg/dL). Sulfonylurea screen and insulin autoantibodies were negative. She had a normal cosyntropin stimulation test. Endoscopic ultrasound and 68 gallium-labelled octreotide positron emission tomography/CT were negative. Methadone was tapered off and she was transitioned to buprenorphine with resolution of the hypoglycaemia the following day. Also described is a brief case of a patient on dialysis and 240 mg of methadone daily who developed episodes of symptomatic hypoglycaemia (up to 1.2 mmol/L) that resolved after methadone dose reduction to 100 mg daily.

Maingi *et al* described a case of a man in his mid 40s with rectosigmoid cancer, renal failure and malabsorption on total parenteral nutrition (TPN) infusion for 18 hours a day.¹⁸ When his fentanyl patient-controlled anesthesia (PCA) for cancer pain was changed to methadone, he developed symptomatic hypoglycaemia that resolved only after methadone infusion was stopped. Gjedsted *et al* presented a similar case of a female child with acute lymphatic leukaemia and cancer pain.¹⁹ When intravenous fentanyl was changed to intravenous methadone and the dose was escalated from 860 mg/24 hours to 1560 mg/24 hours, blood glucose declined from the range of 5.6–11.1 mmol/L (100–200 mg/dL) to 1.1–1.7 mmol/L (20–30 mg/dL). Reduction of the dose of methadone normalised the blood glucose.

Moryl *et al* conducted a chart review of 59 patients on methadone for cancer pain and reported 11 patients with a glucose level <3.9 mmol/L (mean level of 3.0 mmol/L, range of 1.3–3.7 mmol/L) precipitated by dose escalation.²⁰ In a retrospective observational study, Flory and colleagues found a significant increased risk of hypoglycaemia in patients treated with methadone at doses greater than 40 mg/day ($p < 0.01$). Logistic multivariable regression showed a significant association between methadone and hypoglycaemia with an OR of 2.2 (95% CI (1.6–2.9)) and a dose-response relationship with an OR of 3.1 (95% CI (2.5–3.6)) when doses were greater than 80 mg/day.²³

Our study has a few limitations. First, the generalisability of our study is limited as we are only able to draw conclusions from one case. The sensitivity for detecting insulinomas by endoscopic ultrasound is poor (75–83%) and a lesion may have been missed during this examination.²⁸ The gold standard diagnostic test for insulinoma localisation, the selective calcium arterial stimulation test (SACST), was inadequate due to haemolysed samples in the proximal splenic artery, gastroduodenal artery and superior mesenteric artery, which would localise to the head, neck and body of the pancreas, respectively. We did not repeat the SACST because the results of

the hypoglycaemia evaluation during the third supervised fast were available and no longer consistent with an insulinoma (C peptide was <0.6 ng/mL and proinsulin was <5 pmol/L despite a glucose level of 2.7 mmol/L). The insulin level, although drastically decreased over time, is only mildly above the reference range and we believe this is in part related to the poor kidney clearance. Second, when the serum methadone level was undetectable, the patient underwent a short fast of 24-hour duration, which preserved her blood glucose levels in 4.6–5.2 mmol/L (82–93 mg/dL) range. About two-thirds of patients with insulinoma have hypoglycaemia within the first day of fasting and 85–95% have hypoglycaemia within 48 hours.²⁹ We did not pursue the standard 72 hours duration of the fast because we had a low clinical suspicion for an insulinoma and the patient was otherwise ready for hospital discharge.

Hypoglycaemia is now listed as one of the potential adverse effects of methadone in the setting of overdose or dose escalation in the Summary of Product Characteristics.³⁰ Further prospective studies are needed to determine the prevalence of new-onset hypoglycaemia in methadone users in addition to establishing the biochemical cause of hypoglycaemia in diverse patient populations with or without other hypoglycaemic risk factors. We believe providers should consider high doses of methadone as a potential aetiology in a patient with recurrent hyperinsulinaemic hypoglycaemia and consider tapering off methadone prior to undergoing an extensive and invasive insulinoma workup.

Learning points

- ▶ Excess methadone use may clinically present as an insulinoma; however, the annual incidence of insulinoma is 1–4 in one million, whereas the number of methadone prescriptions yearly is increasing.
- ▶ Consider methadone-induced hypoglycaemia in a patient with laboratory evidence of hyperinsulinaemic hypoglycaemia with concurrent use of methadone, in addition to other causes of hypoglycaemia (eg, exogenous insulin use, sulfonylurea ingestion and insulin autoimmune syndrome) ruled out.
- ▶ The gold standard for diagnosis of insulinoma is a selective calcium arterial stimulation test, which is a time-consuming, invasive and costly study. Therefore, consider discontinuing high dose methadone in patients with hyperinsulinaemic hypoglycaemia and re-evaluate fasting glucose levels prior to invasive/extensive workup for insulinoma.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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