JCEM Case Reports, 2025, **3**, luaf041
https://doi.org/10.1210/jcemcr/luaf041
Advance access publication 19 March 2025
Case Report

Hypoglycemia Secondary to Intentional Insulin Poisoning Managed With Intravenous Hydrocortisone

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Abstract

Insulin poisoning, defined as the administration of any dose exceeding therapeutic levels, is a medical emergency that can lead to profound hypoglycemia, resulting in acute and long-term neurological sequalae and death. Current Australian therapeutic guidelines recommend oral or IV glucose as the sole treatment modality for hypoglycemia resulting from insulin poisoning. However, the altered pharmacokinetics of insulin glargine at doses exceeding 0.9 IU/kg can result in prolonged hypoglycemia, often necessitating several days of IV glucose to maintain euglycemia. Although IV glucose is generally considered a benign intervention, its prolonged use can be associated with several adverse effects, including thrombophlebitis, extravasation necrosis, fluid overload, hyponatremia, and glycogenic hepatopathy. To reduce these complications, adjunct therapies such as glucocorticoids, octreotide, glucagon, and surgical excision of subcutaneous insulin deposits have been described in the literature. We report a case of refractory hypoglycemia secondary to insulin poisoning managed with IV hydrocortisone as an adjunctive therapy to IV glucose. To the authors knowledge, this is the first case report describing the use of IV hydrocortisone as a single adjunct in this setting.

Key Words: insulin poisoning, insulin toxicity, hydrocortisone, hypoglycemia

Introduction

Current Australian guidelines recommend oral (PO) or IV glucose as the cornerstone of hypoglycemia management in cases of insulin poisoning [1]. If a target blood glucose level (BGL) of 4 to 8 mmol/L (72-144 mg/dL) (normal reference range, 3.9-5.5 mmol/L; 70-99 mg/dL) cannot be maintained following an initial PO or IV bolus, then 10% or 50% IV glucose infusion is advised [1]. To mitigate the risk of fluid overload and hyponatremia, 50% glucose is preferred if the rate of 10% glucose exceeds 250 mL/h [1]. However, administration of 50% glucose requires a central venous catheter (CVC) to reduce the risk of thrombophlebitis and tissue necrosis [1]. A recent systematic review of 45 cases of insulin poisoning highlighted the role of adjunct therapies not mentioned in Australian guidelines, including glucocorticoids, glucagon, octreotide, and surgical excision of the subcutaneous (SC) insulin deposits [2]. Hydrocortisone, a short-acting glucocorticoid, increases hepatic glucose production and induces insulin resistance reducing glucose uptake into the liver and skeletal muscle [2-5]. Three case reports have detailed its use to manage refractory hypoglycemia secondary to insulin poisoning [3, 4, 6]. To the authors' knowledge, our case report is unique in being the first to describe the use of IV hydrocortisone as a single adjunct therapy to glucose in a patient with diabetes.

Case Presentation

A 27-year-old female was brought in by ambulance to the emergency department several hours after self-administering 3000 units of high-concentration insulin glargine (300 IU/mL, Toujeo) and 300 units of insulin aspart (100 IU/mL, NovoRapid), SC into multiple areas of her abdomen. She denied coingestants. This is on the background of known insulin-dependent monogenic diabetes, diagnosed at age 13 years and managed with gliclazide modified release 120 mg daily and insulin glargine (300 IU/mL) 30 units daily. Other comorbidities included borderline personality disorder and depression with multiple previous suicide attempts involving SC insulin, polypharmacy overdose, and self-harm. Initial capillary BGL was 7.6 mmol/L (136.8 mg/dL) (normal reference range, 3.9-5.5 mmol/L; 70-99 mg/dL) with paramedics. This dropped to 3.8 mmol/L (68.5 mg/dL), managed with PO glucose paste followed by an IV 10% glucose infusion, 100 mL/h, during transfer to hospital.

Diagnostic Assessment

On arrival to the emergency department, capillary BGL was 4.5 mmol/L (81 mg/dL) and Glasgow Coma Scale was 14 with otherwise normal vital signs. Physical examination revealed a mildly tender abdomen without evidence of SC collections of insulin. An initial venous blood gas reported a nadir glucose of 3.1 mmol/L (56 mg/dL) (reference range, 3.9-5.5 mmol/L; 70-99 mg/dL), lactate 1.9 mmol/L (17.1 mg/dL) (reference range, 0.4-2.0 mmol/L; 3.6-18.0 mg/dL), and potassium 3.5 mmol/L (3.5 mEq/L) (reference range, 3.4-4.8 mmol/L; 3.4-4.8 mEq/L). Sulfonylurea, insulin and c-peptide levels were not tested due to collection error.

Treatment

ED management included a continuous IV 10% glucose infusion at 100 mL/h. Six additional 50-mL boluses of 50%

Received: 10 October 2024. **Editorial Decision:** 18 February 2025. **Corrected and Typeset:** 19 March 2025

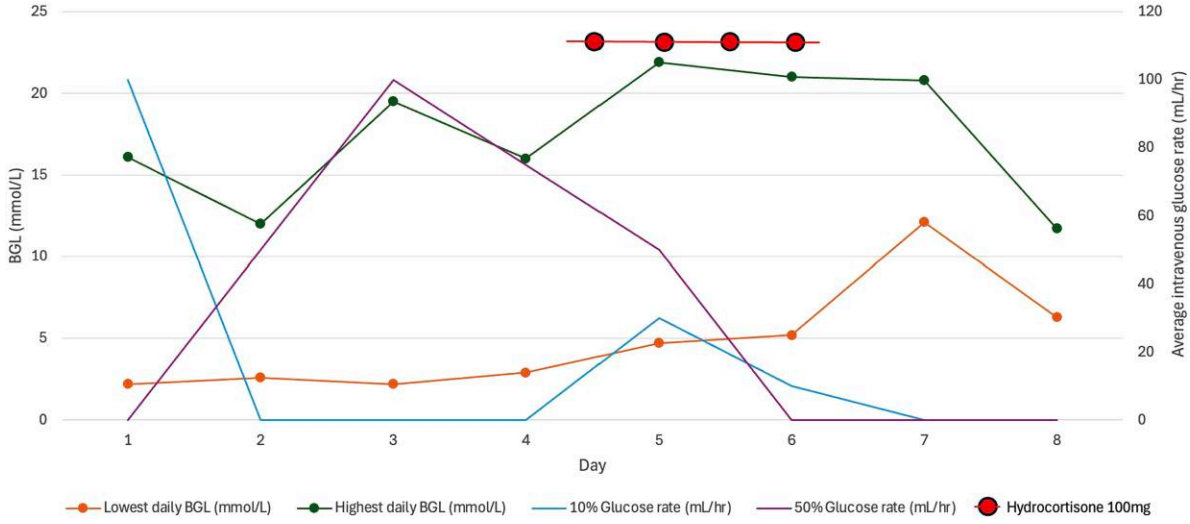

Figure 1. Daily highest and lowest blood glucose level (BGL) (mmol/L), average daily 10% and 50% glucose infusion rates (mL/h), and IV 100-mg hydrocortisone doses.

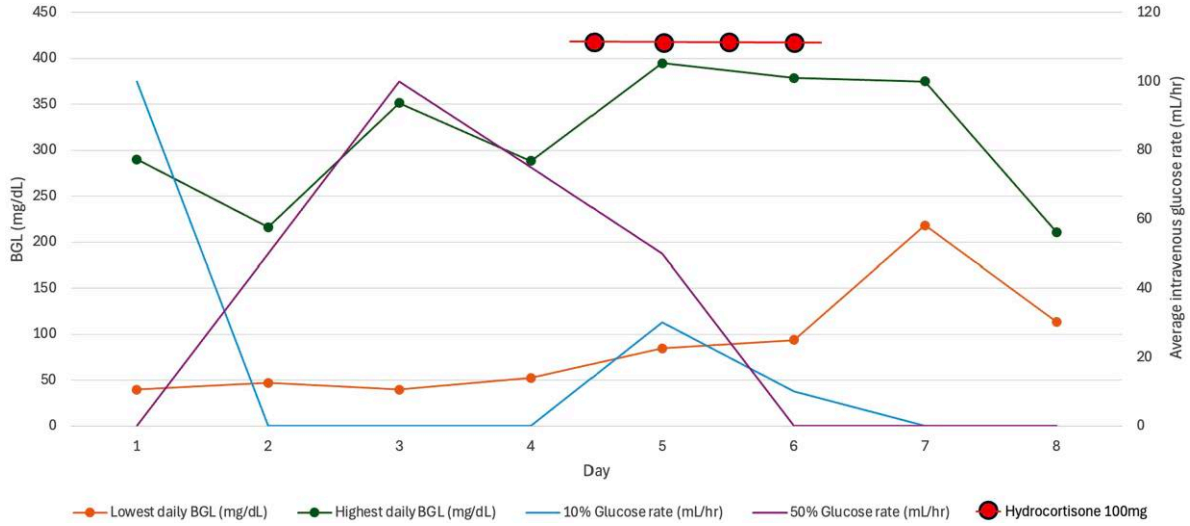

Figure 2. Daily highest and lowest blood glucose level (BGL) (mg/dL), average daily 10% and 50% glucose infusion rates (mL/h), and IV 100-mg hydrocortisone doses.

glucose were required to maintain capillary BGL above 4 mmol/L during the first 6 hours. Given the refractory hypoglycemia, the patient was transferred to the intensive care unit, where a CVC was inserted and a 50% IV glucose infusion was started a rate of 50 mL/h. A total of 80 mmol of IV potassium chloride was required in the first 24 hours. Capillary blood glucose levels and venous blood gases were used for monitoring treatment.

Over the following 3 days, attempts to down-titrate the 50% glucose infusion below 50 mL/h were unsuccessful due to recurrent hypoglycemia with nadir capillary blood glucose of 2.2 mmol/L (39.6 mg/dL) (reference range, 3.9-5.5 mmol/L; 70-99 mg/dL) (Figs. 1 and 2). Oral intake remained poor due to persistent nausea and loss of appetite. On day 4 of admission, the patient developed right upper quadrant pain, worsening nausea, and new marked elevation in aspartate aminotransferase 1141 IU/L (reference range 5-35 IU/L) and alanine transaminase 1007 IU/L (reference range 5-40 IU/L) (Fig. 3). Synthetic liver function was within normal limits and premorbid liver function tests were normal. Further investigations demonstrated a negative viral hepatitis screen and undetectable serum paracetamol levels. An abdominal ultrasound reported mild to moderate hepatosteatosis with no evidence of cirrhosis or biliary pathology. At the end of day 4, with evidence of presumed glycogenic hepatopathy, concerns regarding lower limb edema and a 50% glucose infusion rate between 50 and 100 mL/h, adjunct treatment with IV hydrocortisone 100 mg 4 times per day was commenced (Figs. 1 and 2). IV glucose requirements reduced significantly after the first dose enabling transition to 10% glucose at 30 mL/h after the third dose of hydrocortisone. IV glucose was ceased on day 6 after a total of 4 doses of hydrocortisone (Figs. 1 and 2).

Outcome and Follow up

The patient recommenced regular insulin glargine (100 IU/mL, Optisulin) 30 units daily on day 7. Following clearance from the inpatient consulting psychiatric team, she was

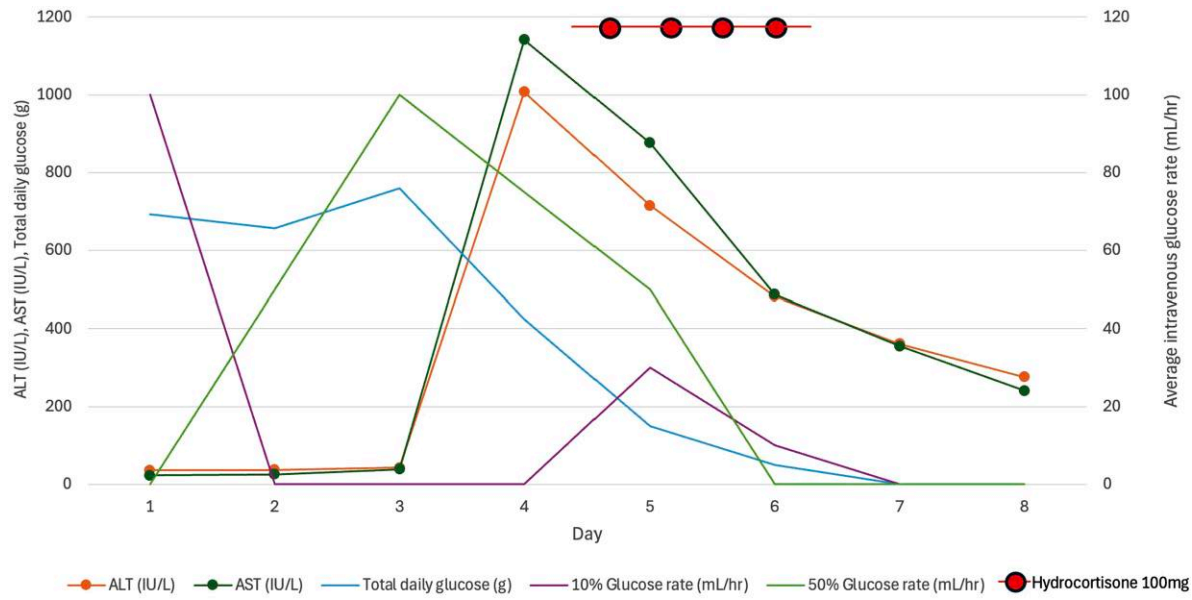

Figure 3. Daily total IV glucose (g), daily aspartate aminotransferase (AST) (IU/L), daily alanine transaminase (ALT) (IU/L), average daily 10% and 50% glucose infusion rates (mL/h), and IV 100-mg hydrocortisone doses.

discharged on day 8 with resolution of right upper quadrant pain and improvement in liver dysfunction, alanine transaminase 276 IU/L (reference range 5-40 IU/L), and aspartate aminotransferase 241 IU/L (reference range 5-35 IU/L) (Fig. 3). Follow up was arranged with the health service outpatient diabetes clinic and community mental health team.

Discussion

At standard doses of 0.4 to 0.9 IU/kg the pharmacokinetics of insulin glargine are well described, reaching maximum serum concentration in 12 to 16 hours and complete metabolism within 24 hours [7]. However, studies suggest the pharmacokinetics of insulin glargine above this dose are highly variable, with reports of hypoglycemic effects lasting for as long as 7 days [2-4, 7, 8]. Although the exact mechanism remains unclear, delayed absorption from the injection site and prolonged clearance of absorbed insulin, secondary to impaired hepatic metabolism and renal clearance, are all thought to contribute [2, 7, 8]. Absorption is thought to be delayed because of the compression of local blood vessels caused by a large volume of fluid within the SC tissue [2, 7, 8]. Furthermore, at plasma insulin concentrations >50 microIU/mL, hepatic glucose production is likely completely inhibited, making patients solely reliant on exogenous sources of glucose [7].

In our case, the patient self-administered 3000 units of insulin glargine (300 IU/mL), equal to 33 IU/kg. Unfortunately, because of a collection error, insulin concentrations on admission could not be determined. Subsequent measurement of insulin levels was deemed unnecessary as it would not alter management, which focused on titrating IV glucose to achieve BGLs between 4 and 8 mmol/L (72-144 mg/dL) (normal reference range, 3.9-5.5 mmol/L; 70-99 mg/dL) [1]. However, on day 4, despite a continuous infusion of 50% glucose at 50 to 100 mL/h and an average 633 g of IV glucose per day, there was ongoing evidence of hypoglycemia. We believe the IV glucose contributed to both glycogenic hepatopathy and lower limb edema, 2 adverse effects reported frequently in other cases of insulin poisoning [2, 9]. We therefore decided to explore other adjunct therapies previously described in the literature, including glucagon, octreotide, surgical resection, and glucocorticoids [2-4, 6]. Glucagon, although frequently prescribed in multiple case reports, theoretically has a limited role in insulin poisoning because it relies on adequate hepatic glycogen stores, which are rapidly depleted [2, 10]. It should only be used in the community when PO glucose cannot be safety given and IV glucose is not available [1, 10]. Octreotide is a long-acting synthetic somatostatin analogue that inhibits endogenous insulin secretion [2-4, 10]. Although it is a recognized treatment modality in sulfonylurea poisoning, case studies have shown inconsistent results in insulin poisoning [2-4, 10]. In those with residual β-cell function, it may reduce endogenous insulin release in response to IV glucose therapy [2, 10]. Given our patient denied any sulfonylurea ingestion and had limited β-cell reserve, it was not prescribed. Although few case reports exist, surgical resection is thought to have a role in cases of visible and accessible areas of insulin infiltrate, which our patient did not have [2]. In this context, glucocorticoids emerge as a logical treatment option given their well-documented side effect of hyperglycemia, mediated through multiple different pathways including increased insulin resistance, enhanced hepatic glucose production, and inhibition of insulin secretion [2-5]. In this case, hydrocortisone was selected over other glucocorticoids because of its shorter half-life, which allowed for more precise titration of BGLs and minimized prolonged exposure to potential side effects, including psychosis [2-5].

To our knowledge, only 3 case reports have described the use of IV hydrocortisone in the management of an insulin overdose [3, 4, 6]. The first documented case in 1993 described the resolution of hypoglycemia in a 16-year-old patient who self-administered 900 IU of mixed insulin (30% neutral/70% isophane) [6]. However, the dose and duration of hydrocortisone was not specified, making it difficult to draw conclusions about its efficacy [6]. Subsequently, 2 additional case reports have detailed the use of hydrocortisone,

but only following other adjunct therapy, including octreotide and glucagon [3, 4]. Both case reports concluded that hydrocortisone contributed to the resolution of hypoglycemia and facilitated the discontinuation of IV glucose and other adjunct therapies [3, 4]. It was further hypothesized that early hydrocortisone therapy may shorten intensive care unit stays, avoid CVC insertion, and prevent fluid overload [4]. Despite these observations, the concurrent use of hydrocortisone with other therapies limits the ability to ascertain its true efficacy in this context. Importantly, as in our case, no short-term side effects, such as hypertension or psychosis, were reported [3, 4, 6].

In conclusion, our case uniquely describes the use of IV hydrocortisone as a single adjunct therapy used after treatment with IV glucose monotherapy in a patient with significant insulin poisoning. Although it is difficult to predict whether hypoglycemia resolved because of the clearance of exogenous insulin alone or the effect of hydrocortisone, this case supports the use of hydrocortisone in the management of hypoglycemia secondary to insulin poisoning. Clinicians should be aware of the adjunct therapies available to assist in the management hypoglycemia following insulin poisoning requiring prolonged IV glucose therapy.

Learning Points

- IV glucose is associated with several adverse effects, including thrombophlebitis, extravasation necrosis, fluid overload, hyponatremia, and glycogenic hepatopathy.
- Hydrocortisone can be a useful adjunct therapy to IV glucose in the management of refractory hypoglycemia secondary to insulin poisoning.
- Australian guidelines need to be updated to further support clinicians in the management of an insulin poisoning—particularly regarding refractory hypoglycemia requiring prolonged IV glucose therapy.

Contributors

All authors made individual contributions to authorship. All authors reviewed and approved the final draft.

Funding

No public or commercial funding was obtained for this study.

Disclosures

The authors declare that they have no conflict of interest.

Informed Patient Consent for Publication

Signed informed consent obtained directly from patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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