Prolonged Severe Hypoglycemia in a Pediatric Patient With Type 1 Diabetes

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Case Presentation

A 13-year-old girl with type 1 diabetes presented to the emergency department (ED) after being found unresponsive at home by her mother with a capillary blood glucose (CBG) of 1.488 mmol/L (26.8 mg/dL) (Figure 1). She was given intramuscular (IM) glucagon and intravenous (IV) dextrose by emergency medical services, and her CBG increased to 4.628 mmol/L (83.4 mg/dL) by the time of her ED arrival.

At presentation, she was diaphoretic and somnolent, with an otherwise unremarkable exam, body temperature 37°C (98.6°F), heart rate 93 beats/min, respiratory rate 22 breaths/min, blood pressure 103/62 mmHg, and oxygen saturation 99%. Other significant admission laboratory values were sodium 139 mmol/L, potassium 3.6 mmol/L, carbon dioxide 23 mmol/L, creatinine 32 µmol/L, magnesium 0.86 mmol/L, phosphorus 1.35 mmol/L, alanine aminotransferase 95 units/L, and aspartate aminotransferase 75 units/L.

While in the ED, her CBG value repeatedly fell to <2.7 mmol/L (48.6 mg/dL), requiring multiple IV dextrose boluses and a rapid increase in her continuous dextrose infusion over 3 hours from a glucose infusion rate (GIR) of 2–3 to a high of >10 mg/kg/min to maintain euglycemia. She was admitted to the intensive care unit (ICU) for further management and careful monitoring.

In the ICU, she received intermittent doses of IM glucagon (1 mg each) because of continued hypoglycemia even on continuous dextrose infusion with a GIR of 10 mg/kg/min

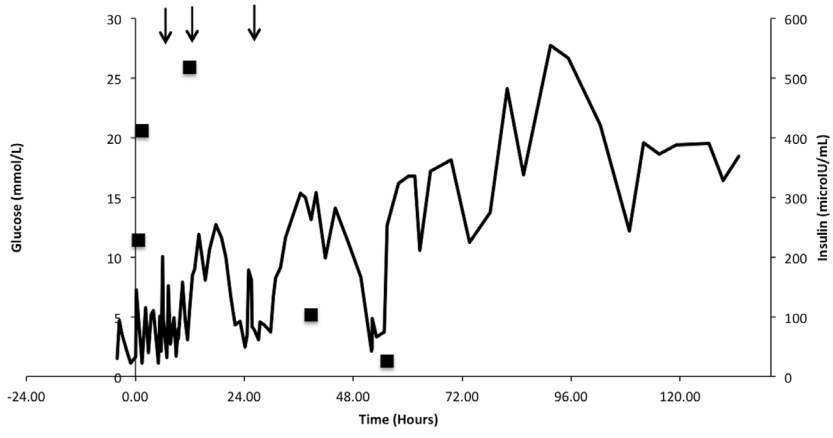

FIGURE 1. Timeline of glucose and insulin levels during admission. The line is glucose levels, squares are insulin levels, and arrows indicate times of glucagon doses given, 1 mg each.

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(Figure 1). With her first glucagon dose, her glucose level rose from 2.09 mmol/L (37.7 mg/dL) to 9.97 mmol/L (179.6 mg/dL) after 20 minutes. On hospital day 2, her dextrose infusion was slowly weaned. At 55 hours from admission, her dextrose infusion was discontinued, and she maintained euglycemia with frequent oral intake. Her glucose level dropped again to 3.0 mmol/L (54.1 mg/dL) overnight with decreased oral intake. At 60 hours, she experienced postprandial hyperglycemia to >16.5 mmol/L (297.3 mg/dL) without any further hypoglycemia, so short-acting insulin was restarted with meals. The following day, long-acting insulin was restarted because of persistent hyperglycemia.

Our patient was diagnosed with type 1 diabetes at age 11 and was on a multiple daily injection insulin regimen of glargine every 24 hours and lispro with meals. Three weeks before admission, her A1C was 13.8%. Initially, her mother reported that she had received no insulin for 3 days and that her last dose of glargine was 1 week earlier because of hypoglycemic episodes at home.

Upon arrival to the ED, evaluation for the cause of her hypoglycemia revealed an undetectable C-peptide and low β-hydroxybutyrate and free fatty acid levels. A cortisol level was 265 nmol/L, adrenocorticotropic hormone was 6.4 pmol/L, lactate was 1.5 mmol/L, and serum amino acids, urine organic acids, and acylcarnitine profile were normal. She had a negative urine drug screen; undetectable ethanol, acetaminophen, and salicylate levels; and urinalysis positive for glucose but negative for ketones. Her thyroid function was normal.

Two insulin levels were drawn shortly after admission, one for the "critical sample" while she was hypoglycemic to 1.1 mmol/L (19.8 mg/dL) and the other a random level while her glucose was 4.8 mmol/L (86.5 mg/dL), but the results did not return for 12 hours. Once available, the insulin level was 228 µIU/mL on the random sample and 412 µIU/mL on the critical sample, about 40 minutes apart. A third insulin level about 12 hours later was 512 µIU/mL (Figure 1). After we disclosed the insulin levels to the patient's mother, she discovered an empty injectable pen of glargine in the patient's bag. The patient never admitted to intentional insulin overdose, but this discovery meant that she may have received up to 300 units of undisclosed insulin glargine. Her insulin level was tracked through her hospitalization and decreased to 25 µIU/mL about 55 hours after admission.

She was evaluated by psychiatry and determined to be safe for discharge home with her mother on hospital day 6.

Questions

1. What side effects can be seen with a long-acting insulin analog overdose?
2. How long is the duration of effect of long-acting insulin analog when given in high doses?
3. How do you treat a long-acting insulin overdose?

Commentary

This case describes the course of an adolescent with type 1 diabetes who had profound and severe hypoglycemia despite reporting no insulin administration for the days preceding admission. Despite this claim, a number of factors pointed to insulin overdose. Even before the insulin levels returned from the laboratory, she had low β-hydroxybutyrate and free fatty acid levels with negative ketones on admission, indicating the likely presence of insulin in her body preventing lipolysis and ketosis. The requirement of such a high GIR, five to six times the usual fasting requirement, also supported the diagnosis of high circulating levels of insulin. Finally, the robust response of her glucose level to glucagon administration was also consistent with the presence of insulin in her body. Her undetectable C-peptide level was consistent with her diagnosis of type 1 diabetes and inability to make endogenous insulin. With her massively elevated insulin level, these findings pointed to exogenous insulin administration.

Symptomatic hypoglycemia is the most commonly encountered presenting feature of an insulin overdose. Patients presenting with severe hypoglycemia due to an insulin overdose also often have hypokalemia, hypophosphatemia, and hypomagnesemia (1,2). Although our patient's potassium level was in the low end of the normal range, the rest of her levels were normal despite her profound hypoglycemia. A number of other complications have been reported after an overdose of insulin, including hypoglycemic encephalopathy, permanent cognitive dysfunction, acute pulmonary edema, acute hepatic injury, seizures, coma, and death (2–6). Our patient had mildly elevated liver transaminases on ED admission, but this was attributed to her history of poorly controlled diabetes, and the levels were not remeasured during her hospitalization. She had no signs or symptoms of concern for the other more severe complications of an insulin overdose.

A very important aspect of this patient's course was the prolonged duration of hypoglycemia, which took about 60 hours to resolve. Insulin glargine typically has a 24-hour duration of action and is taken as a once-daily injection, yet her hypoglycemia lasted much longer. Case reports and pharmacodynamics studies have demonstrated that the pharmacokinetics of all insulins change depending on the dose administered. This is especially true for the long-acting insulin analogs, which have been shown to have an effect up to four times their normal duration (3,5,7–14). The reason for this prolonged effect is postulated to be the result of delayed absorption of a large dose of insulin, or the "depot effect," and/or slower dose-dependent absorption of subcutaneous depot injections (11,15–18). Others have speculated that this may be because

of decreased metabolism of insulin in older individuals with renal impairment or because of delayed absorption with local lipodystrophy (11,19,20). This case demonstrates that a prolonged effect of high-dose insulin glargine occurs even in otherwise healthy young patients without endogenous insulin production and with normal insulin metabolism. In this case, the effect of the additional insulin glargine the patient received lasted almost 4 days, whereas the typical duration of insulin glargine is usually about 24 hours (21).

The mainstay of therapy to treat hypoglycemia from an insulin overdose is treatment and prevention of hypoglycemia with IV dextrose. Electrolyte repletion is also often necessary. Frequent monitoring of glucose levels is recommended to determine the duration of hypoglycemia, especially because the actual duration of most insulins is unknown after administration in excessively high doses (9,18). Care must be taken not to correct the hypoglycemia too aggressively with dextrose infusion because the treatment, rather than the hypoglycemia itself, has been implicated as the cause of acute pulmonary edema and hepatic steatosis in some cases (2,4–6). We obtained serial insulin levels in our patient and noticed a decrease in the level daily after 12 hours from admission. By the time the measured insulin level had decreased to near-normal levels, her hypoglycemia had resolved, with a decreased need for dextrose support.

Our patient's insulin level increased after admission before it decreased. The delay in peak insulin level may be the result of delayed absorption of large doses and may contribute to the prolonged hypoglycemic effect. We therefore recommend monitoring insulin levels as a guide to treatment and for appropriate reintroduction of insulin. We also recommend introducing short-acting insulin first during de-escalation of therapy (11,18).

Besides dextrose infusion to treat hypoglycemia, a number of other treatments have been used for insulin overdose, including glucagon, octreotide, uncooked cornstarch, and surgical excision of the insulin depot. Glucagon raises blood glucose levels quickly by releasing glycogen stores from the liver and is also used in diagnosing hyperinsulinism (22). This was successfully used in our patient and also supported the diagnosis of insulin overdose, despite the denial that the patient had taken any insulin for many days. There is some concern that glucagon may cause rebound hypoglycemia by stimulating endogenous insulin secretion, but this would not be expected in a patient with type 1 diabetes (9,19). Octreotide, a somatostatin analog, decreases endogenous insulin production by the pancreas and has been used in patients with type 2 diabetes and those without diabetes with an insulin overdose (9,15,19). This would not have been effective in our patient with type 1 diabetes. Uncooked cornstarch was effective in a healthy adolescent female after an insulin overdose to prevent nocturnal hypoglycemia (14) but was not attempted in our patient. Finally, some reports of surgical excision of the insulin depot site have been successful in decreasing the degree and duration of hypoglycemia from an insulin overdose but this would only work if the site of a single large dose of injected insulin was known, which was not the case in our patient (4,19).

Clinical Pearls

- When long-acting insulin analogs such as insulin glargine are taken in excessively high doses—even in a young patient with normal insulin metabolism and no endogenous insulin—the duration of action is much longer than is typical with normal-sized doses.
- All patients who receive excessively high doses of long-acting insulin may require inpatient monitoring and prolonged IV glucose therapy.
- Premature reintroduction of insulin should be avoided because the hypoglycemic state can last much longer than expected; serial monitoring of insulin levels is helpful in guiding therapy.
- Recognition of the prolonged duration of long-acting insulin taken in excess is important with the recent introduction of several new long-acting insulin analogs for the treatment of type 1 diabetes.
- Insulin overdose should always be considered in pediatric patients with type 1 diabetes who are experiencing unexplained hypoglycemia, even without disclosure by the patient.

Duality of Interest

No potential conflicts of interest relevant to this article were reported

Previous Publication

An abstract of this case study was published and presented in poster format at the Endocrine Society annual meeting, Orlando, Fla., April 2017.

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