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CASE REPORT

Persistent Hyperinsulinemia Following High-Dose Insulin Therapy: A Case Report

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Abstract

Introduction Overdoses of beta-adrenergic antagonists and calcium channel antagonists represent an uncommonly encountered but highly morbid clinical presentation. Potential therapies include fluids, calcium salts, vasopressors, intravenous lipid emulsion, methylene blue, and high-dose insulin. Although high-dose insulin is commonly used, the kinetics of insulin under these conditions are unknown.

Case Report We present a case of a 51-year-old male who sustained a life-threatening overdose after ingesting approximately 40 tablets of a mixture of amlodipine 5 mg and metoprolol tartrate 25 mg. Due to severe bradycardia and hypotension, he was started on high-dose insulin (HDI) therapy; this was augmented with epinephrine. Despite the degree of his initial shock state, he ultimately recovered, and HDI was discontinued. Insulin was infused for a total of approximately 37 hours, most of which was dosed at 10 U/kg/hour; following discontinuation, serial serum insulin levels were drawn and remained at supraphysiologic levels for at least 24 hours and well above reference range for multiple days thereafter.

Conclusion The kinetics of insulin following discontinuation of high-dose insulin therapy are largely unknown, but supraphysiologic insulin levels persist for some time following therapy; this may allow for simple discontinuation rather than titration of insulin at the end of therapy. Dextrose replacement is frequently needed; although the duration is often difficult to predict, prolonged infusions may not be necessary.

Keywords High dose insulin · Overdose · Beta-blocker · Calcium channel-blocker · Poisoning

Introduction

Toxicity from calcium channel antagonist and beta-adrenergic antagonist overdose is an uncommonly reported problem associated with high morbidity and mortality; together, calcium channel antagonist and beta-adrenergic antagonists were associated with about 8.8% of fatalities as reported to US poison control centers in 2017 despite cardiovascular medications representing only 4.2% of total exposures and 6.4% of adult exposures [1]. Therapy with calcium, pacing, and atropine produces variable responses in human case series [2]. Vasopressor therapy is frequently used; however, animal evidence suggests the possibility of harm when used in the setting of beta-blocker toxicity without inotropic support [3, 4]. Due to these limitations, therapy with high-dose insulin (HDI) has been increasingly recognized as beneficial [5, 6]. During this therapy, large doses of insulin (1–10 U/kg/hour) are infused to produce a positive inotropic effect [5, 7]. Animal models of toxicity and human case series support HDI use in the management of poison-induced cardiogenic shock [2, 7–10]. Although this therapy appears effective, risks include potentially significant hypokalemia and hypoglycemia [6].

Supplemental dextrose is often required after discontinuing HDI, sometimes for 24 hours or more [5]. Scant literature exists describing insulin kinetics in vivo after HDI. We report a case of persistently elevated insulin levels after HDI and discuss the implications for the duration of supplemental dextrose.

Case Report

A 51-year-old 100-kg (BMI 27.96 kg/m^2) man with a history of hypertension and alcohol dependence (and not known to be diabetic) presented to a rural hospital approximately 2 hours

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after ingesting, by his report, approximately 40 tablets of an uncertain mix of his own 25 mg metoprolol tartrate and his wife's 5 mg amlodipine in a suicide attempt. He was alert but vomiting on presentation. Initial vital signs included heart rate from 50 to 60 beats per minute and systolic blood pressure of 100 mmHg. He was given 3 g calcium gluconate and a 1 U/kg bolus of intravenous regular insulin followed by a 1 U/kg/hour insulin infusion. Blood glucose prior to insulin bolus was 124 mg/dL and thus, 150 mL of 50% dextrose solution was administered with the insulin bolus; additionally, a 10% dextrose infusion was started at 250 mL/hour. Transfer to a tertiary care hospital was requested by the initial facility. Prior to the transfer, the patient was intubated by flight medics for a depressed level of consciousness; this was accomplished with etomidate and succinylcholine.

On arrival at 4 hours post-ingestion, blood pressure was 79/49 mmHg and heart rate was 38 beats per minute. His blood pressure reached a nadir of 55/45 mmHg with heart rate nadir of 30 beats per minute within 15 minutes of arrival at the tertiary facility. Insulin infusion was then titrated up by 1 U/kg/hour approximately every 15 minutes to a max of 10 U/kg/hour over the 2 hours after arrival to the tertiary facility (6 hours post-ingestion); this resulted in improvement in systolic blood pressure to 80–90 mmHg. An epinephrine infusion was started at 0.2 mcg/kg/minute approximately 20 minutes after arrival at the tertiary facility. During the titration of insulin, the blood glucose was checked once every 15 minutes. When a maximal dose of 10 U/kg/hour was reached, blood glucose was checked approximately once every 30–60 minutes. Dextrose was initially provided via IV route at a rate of 150 mL of 50% dextrose infusion; this was titrated down to 75 mL/hour in 25 mL/hour increments every 2 hours starting at approximately 11 hours post-ingestion; for the remainder of the HDI therapy course, 50% dextrose was infused at rates between 50 and 75 mL/h.

HDI infusion continued at 10 U/kg/hour and epinephrine at 0.2 mcg/kg/minute until the patient stabilized at approximately 30 hours post-ingestion. During HDI infusion, serum potassium was monitored hourly with only one episode of hypokalemia (serum potassium 3.4 mEq/L) noted; this occurred at the time of presentation to the tertiary facility and was treated with 20 mEq of IV potassium. During the remainder of HDI therapy, there were no additional episodes of hypokalemia and no additional potassium supplementation was required. From 30 to 32 hours post-ingestion epinephrine was weaned, and from 33 to 39 hours post-ingestion, the insulin was weaned; the total duration of HDI therapy was approximately 37 hours. Serum creatinine peaked at 2.57 mg/dL approximately 27 hours post-ingestion but normalized by 50 hours post-ingestion; there was no evidence of hepatic injury during the patient's course. Following discontinuation of HDI, 50% dextrose infusion was continued for 65 hours, followed by a 10% dextrose infusion for 5 days, then 5% dextrose for two more days. Enteral feeding was started on hospital day five, providing 2160 kcal daily. During this time, no hypoglycemic episodes were noted; blood glucose nadir was 80 mg/dL. The patient made a full recovery.

After discontinuing HDI, serial insulin levels were obtained. Initially, > 1000 μU/mL (normal range 2.6–24.9 μU/mL), insulin concentrations trended down over 7 days (see Fig. 1 and Table 1; values after 144 hours were not shown but ranged 8.8–33.3 mU/mL). During this time, serum glucose was measured approximately every 1–2 hours (see Fig. 1). A drop in blood glucose from 175 to 88 occurred at 48 hours post-HDI discontinuation and coincided with a decrease in the dextrose infusion from 25 to 12.5 g/h; this prompted an increase in the infusion rate back to 25 g/h. C-peptide concentration was 3.62 ng/mL at 66 hours post-HDI (reference range 1.10–4.40 ng/mL). There was one additional hypokalemic episode on hospital day 6 (serum potassium 3.4 mEq/L) that was treated with 40 mEq oral potassium. There were no episodes of hyperkalemia. Serum magnesium was checked daily with a single episode of hypomagnesemia (serum magnesium 0.9 mEq/L) on hospital day 2. Serum phosphorus was not checked in a serial fashion.

Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Discussion

To our knowledge, persistently elevated serum insulin levels have not been reported following HDI [6]. This finding corroborates clinical experience that dextrose infusion is commonly required for up to 2 days following discontinuation of HDI [6]. Further studies are needed to identify factors (e.g., dose, duration of treatment, kidney/liver injury, and endogenous insulin production) that influence this phenomenon.

Serum insulin increases following oral and intravenous dextrose administration [11]. In an early study of pancreatic response to intravenous and oral dextrose administration, peak serum insulin levels following oral dextrose ranged from approximately 60 to 220 μU/mL; following intravenous dextrose, administration peak levels were lower, ranging from approximately 30 to 100 μU/mL [11]. In another study, concurrent intravenous dextrose infusion and oral dextrose administration caused a rise in serum insulin to approximately 200 μU/mL by 4 hours after infusion initiation [12]. In the context of these studies, the persistently elevated serum insulin levels in this case were likely secondary, in part, to endogenous insulin secretion stimulated by dextrose infusion and enteral feeding. This complicates the determination of post-therapy pharmacokinetics of HDI, as the relative contributions of endogenous and exogenous insulin are unknown; additionally, the first two levels obtained were above the upper detection limit (1000 μU/mL) of our assay.

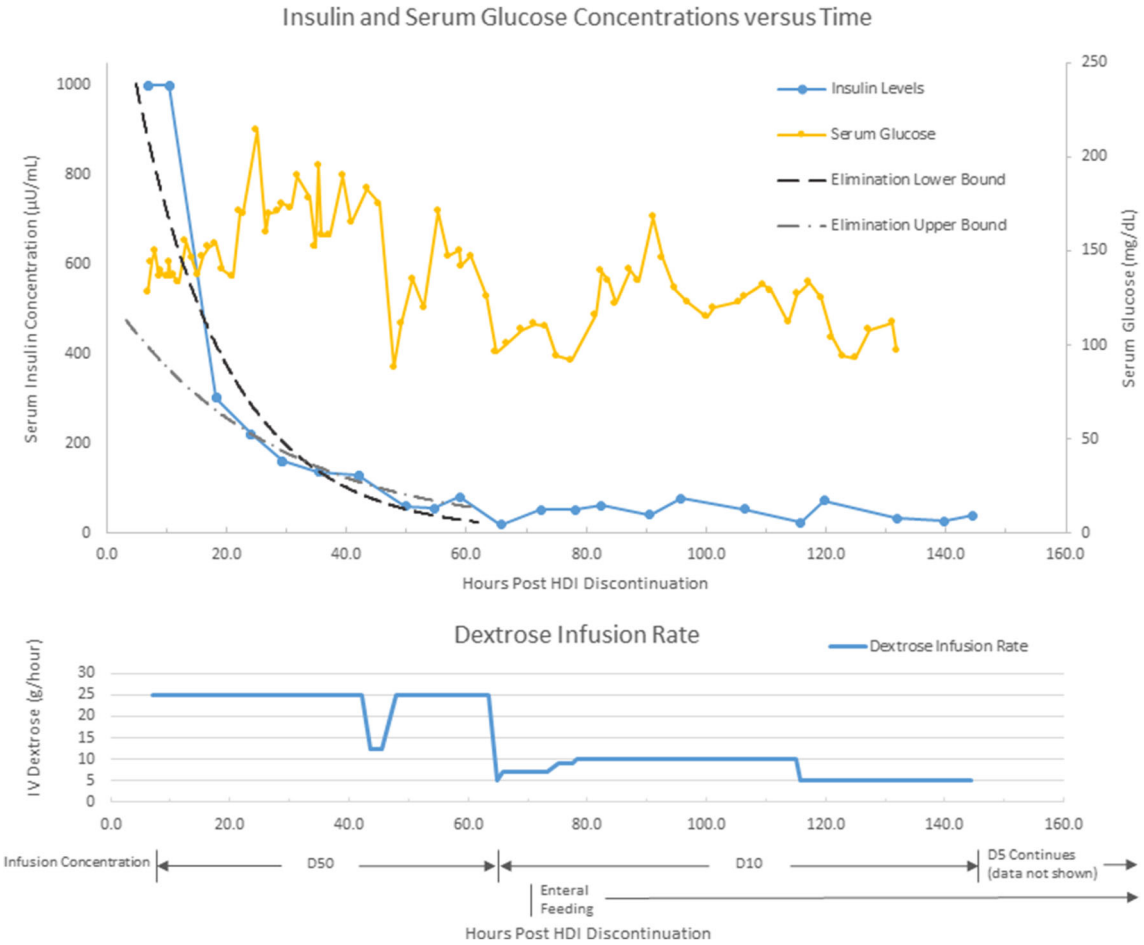

Fig. 1 Graphs of serum insulin concentration, serum glucose concentration, and infused dextrose rate and concentration versus time elapsed since HDI discontinuation.

With these limitations in mind, we attempted to determine the apparent half-life of insulin by fitting an exponential curve to the data that represented both the shortest and longest plausible half-lives (see Fig. 1, elimination lower bound and elimination upper bound, respectively). We observed that there appeared to be three separate segments to the insulin versus time graph. In the first 20 hours, we observed a rapid decline that may have represented either distribution or elimination of insulin, and thus, it is unclear whether the two initial greater than 1000 μU/mL levels represent outliers or not. Following

Table 1 Table of serum insulin concentrations with time elapsed since HDI discontinuation.

Hours post-HDI	Serum insulin concentration (μU/mL)	Hours post-HDI	Serum insulin concentration (μU/mL)
6.9	> 1000	72.5	52.7
10.5	> 1000	78.2	52.7
18.3	301.3	82.6	62.4
24.1	220.5	90.6	41.2
29.3	160.2	95.8	78
35.4	135.8	106.4	53.2
42.0	129	115.8	22.7
49.8	59.4	119.7	72.9
54.7	55.8	131.9	33
58.9	80.5	139.8	26.1
65.7	18.1	144.6	39.8

this, there was apparent exponential decay until about 60 hours post-therapy. In the terminal segment of the graph, the levels fluctuate within a physiologically plausible range for days. We presumed that the first several insulin levels represented mostly exogenous insulin as they were well above the concentrations in the aforementioned intravenous and oral dextrose loading studies [11, 12]. Thus, we presumed that the decreasing levels early after HDI discontinuation represented clearance of the exogenous insulin, while the long tail observed represented mostly endogenous insulin. Using these observations, we fit an exponential curve to the first 7 insulin levels (6.9–42 hours post-therapy) as the shortest reasonable estimation of the half-life (this assumed the first two points were not outliers). We also fit an exponential curve to the segment of the graph where there appears to be exponential decay minus the first two (potential outlier) values (from 18.3–42 hours post-therapy) and considered this the longest reasonable half-life. Under these assumptions, the apparent half-life of insulin in this case was between 10.6 and 18.7 hours; the lower bound would be shorter if the initial two insulin levels were significantly greater than 1000 μU/mL. After the initial elimination phase, we observed a prolonged phase with insulin levels above the fasting reference range, although still within a physiologically plausible range. This is best explained by ongoing endogenous release secondary to continued oral and intravenous dextrose administration; the endogenous contribution to total insulin was inferred from a by-product of insulin production, c-peptide, which was measured once at 66 hours post-HDI and found to be within the physiologic range.

Although the determination of endogenous and exogenous contributions to serum insulin was not possible, the decline in serum insulin concentration suggests that earlier discontinuation of IV dextrose may be reasonable. The insulin dosing in this case was the maximum that is typically used [7]. Despite this, serum insulin concentrations fell to physiologically plausible ranges within 24–30 hours following discontinuation. During the course of this case, several blood glucose readings in the 80–90 mg/dL range prompted increases in the dextrose infusion rate. However, the lack of hypoglycemia in this case and decline in insulin levels indicate that prolonged dextrose infusion may not have been required. Presuming no hypoglycemic episodes, dextrose infusion may be discontinued more rapidly, perhaps as early as 24 hours after HDI discontinuation. Frequent blood glucose monitoring following cessation of intravenous dextrose would allow for prompt recognition of resultant hypoglycemia.

This case presents additional implications regarding discontinuing the insulin infusion. Under normal dosing conditions, intravenous regular human insulin has a half-life of 6.5–9 minutes [13]. In our patient, insulin levels remained above the physiologic range for the first 24 hours and were above the upper detection limit for our assay until 10 to 18 hours post-infusion. To our knowledge, no protocol-driven method of discontinuing HDI exists; standard practice varies from titration, as in this case, to discontinuing without titration. While extrapolation from the levels obtained in this single case to clinical practice is obfuscated by the lack of an established relationship between serum concentration and inotropic effect, the supraphysiologic levels in the first 18 hours post-discontinuation lend some supporting evidence that titration of insulin may not be necessary. We observed in this case that a significant amount of exogenous insulin remains well after the insulin infusion is discontinued; thus, there may continue to be a positive inotropic effect well after the insulin infusion is discontinued. Titration of the insulin infusion rather than simple discontinuation once the patient is stable could lead to a longer duration of need for supplementary dextrose and blood glucose monitoring, but a prospective study is needed to determine the optimal discontinuation method.

Conclusion

Insulin kinetics following HDI therapy are unpredictable, and concentrations may remain high for days after cessation of HDI. Discontinuation of HDI and dextrose infusions requires careful monitoring. However, titration of HDI and prolonged dextrose infusion may not be required; it may be possible to simply discontinue HDI once hemodynamic stability is achieved, and dextrose infusions may be weaned potentially as early as 24–48 hours post-therapy if appropriate hemodynamic and blood glucose monitoring are maintained.

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Compliance with Ethical Standards

Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Conflict of Interest None

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